JUHA NISSINEN

DETERMINANTS OF OUTCOME IN ADULT CARDIAC SURGERY

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‘To the Heart Team in Vaasa.’

CONTENTS

ABSTRACT

A total of 4,563 adult patients underwent cardiac surgical procedures at Vaasa Central Hospital from January 1994 to June 2008. A substantial amount of data from all the patients was prospectively collected in an institutional database, including both cardiac examinations and surgical care. This material was later retrospectively analysed in five studies. The main focus of these studies was on recognizing specific risk factors related to various cardiac surgical procedures.

The first two studies evaluated the risk predicting value of preoperative spirometry. In the first one we showed that impaired left ventricular function (EF<50%) is strongly associated with preoperative low percentages of forced vital capacity (FVC<80%) in a material of 453 patients undergoing aortic valve reconstruction (AVR). The same association was not found with forced expiratory volume in 1 second (FEV1). Preoperatively lowered FVC (FVC<80%) had a better prognostic value for postoperative death in AVR patients than preoperatively lowered FEV1 (FEV1<75%). Also, the lowered FVC had a clear predictive value for adverse neurologic events and prolonged postoperative stay in the intensive care unit (ICU). The second study ascertained the prognostic value of preoperative spirometry among 1,848 patients undergoing coronary bypass surgery (CABG). The percentages of predicted FVC and of predicted FEV1 were associated with in-hospital death, combined adverse end-point, need for postoperative de novo dialysis, neuropsychological disturbances, atrial fibrillation as well as length of stay in the intensive care unit ≥ 5 days. Only percentage of predicted FVC < 70% along with pulmonary disease but not percentage of predicted FEV1 < 70%, were independent predictors of late overall mortality.

The prevalence of people aged 80 years or over is steadily increasing. The third study included a consecutive series of 247 patients aged 80 years or over who

underwent isolated CABG. They belonged to a series of 3,474 patients who underwent isolated CABG during the same study period. Of them 40% were women (24% among the younger age group). A special focus was on the long-term survival (5 years) of these patients and on risk factors contributing to it. Both univariate analysis and regression analysis showed that diabetes, extracardiac arteriosclerotic disease, neurologic dysfunction, recent myocardial infarction and critical preoperative status were associated with poorer long-term outcome. The 30-day in-hospital mortality in this material was 4.7% compared to 1.3% in the younger age group. The 5-year survival rate was 77% and the 10-year survival 35% (compared to 90% and 76% in the younger group). A propensity score analysis between matched pairs of patients aged 80 years or over and under 80 years showed parallel survival curves between these two groups up to five years after the greater initial 30-day mortality of older patients.

There is longstanding evidence confirming that a long aortic cross-clamp time (XCT) and a long cardiopulmonary bypass time (CPBT) are strong risk factors connected to heart surgery. In our fourth study both XCT and CPBT were cut in cohorts of 30-minute intervals. Both XCT and CPBT were included separately into a statistical regression model in proportion to changes in mortality rate. The best cutoff values of increasing risk were 150 min for XCT and 240 min for CPBT (adjusted for additive EuroSCORE and complexity of the operation). It is worth noting that these cutoff values, despite having a high accuracy (over 90%), have a very low sensitivity (34% for XCT and 28% for CPBT). Thus long XCT and CPBT do not automatically indicate a dismal prognosis. XCT and CPBT have, however, a marked impact on postoperative morbidity. The strong association between postoperative stroke and XCT as well as CPBT is of particular interest. In this series, CPBT was a much stronger predictor of 30-day mortality than XCT.

EuroSCORE, established in 1999, is the most popular and widely validated risk-scoring system in Europe. It is known that EuroSCORE tends to overestimate mortality in low-risk patient groups and to underestimate the risk in very high-risk patient groups. In the original EuroSCORE, non-CABG surgery was calculated as a risk. Thus a simple AVR carries greater risk than a CABG with several bypasses. On the other hand, the complexity of the operation and the severity of the non-cardiac illnesses of the patient are not fully evaluated. In the fifth study we created a new model for risk evaluation (Modified EuroSCORE). More attention was paid to preoperatively impaired renal function by estimating the glomerular filtration rate. Also, the complexity of the operation was taken into consideration. Not surprisingly, this model fitted our material well in Vaasa. The model was tested and validated in Tampere University Hospital (study VI), with an adult cardiac surgery material of 4,014 people, operated from January 2004 to December 2008. Here, the predicted mortality rates with the Modified EuroSCORE were rather similar to those observed. This was not the case for EuroSCORE. Interestingly, the accuracy of the modified score was particularly evident in high risk patients.

TIIVISTELMÄ

Abstract in Finnish

Vaasan keskussairaalassa leikattiin kaikkiaan 4563 aikuissydänkirurgista potilasta tammikuun 1994 ja kesäkuun 2008 välisenä aikana. Huomattava määrä sekä kardiologisiin tutkimuksiin että kirurgiseen hoitoon liittyvää tietoa kerättiin prospektiivisesti kaikista potilaista sairaalan sisäiseen rekisteriin. Tätä rekisterimateriaalia käytettiin myöhemmin retrospektiivisiin analyyseihin viidessä eri tutkimuksessa. Yksi tarkastelun päänäkökulmista oli leikkaukseen liittyvien määrättyjen riskitekijöiden parempi tunnistaminen. Kahdessa ensimmäisessä työssä tutkittiin preoperatiivisen spirometrian leikkausriskiä ennustavaa arvoa. Ensimmäisessä tutkimuksessa todettiin 453 aortaläppäleikkauksen läpikäyneen potilaan materiaalissa alentuneen vasemman kammion funktion (EF< 50%) assosioituvan spirometriassa mitattuun alentuneeseen vitaalikapasiteettiin (FVC< 80%). Samaa yhteytä ei havaittu mitatun sekuntikapasiteetin (FEV1) suhteen. Ennen leikkausta mitatulla alentuneella vitaalikapasitettiarvolla (FVC< 80%) oli parempi aortaläppäleikkaukseen liittyvä ennustearvo kuin alentuneella sekuntikapasiteettiarvolla (FEV1< 75%). Samoin alentuneella FVC:llä oli selvä ennustearvo aivotapahtumien ja pitkittyneen leikkauksen jälkeisen tehohoidon suhteen. Toisessa tutkimuksessa selvitettiin ennen leikkausta mitattujen spirometria-arvojen ennusteellista merkitystä 1848 sepelvaltimo-ohistuspotilaan (CABG) joukossa. Sekä alentunut sekuntikapasiteetti että vitaalikapasiteetti ennustivat sairaalakuolemaa, haitallisia yhdistettyjä päätetapahtumia, leikkauksen jälkeisen munuaiskorvaushoidon tarvetta, neuropsykologisia häiriöitä, eteisvärinää ja pitkittynyttä tehohoitoa ($\geq$5 vrk). Kuitenkin vain alentuneella vitaalikapasiteettiarvolla (<70%) oli keuhkojen laajentumataudin (COPD) ohella merkitystä pitkäaikaisennusteen (10 v.) kannalta.

Koska yli 80 v. täyttäneiden vanhusten osuus sydänleikkausmateriaaleissa on jatkuvasti kasvamassa (15% tässä materiaalissa), haluttiin kolmannessa työssä selvittää tämän potilaskohortin riskiä. Tutkimukseen otettiin 274 peräkkäistä yli 80-vuotista sepelvaltimo-ohitusleikkaukseen tulevaa potilasta. He olivat osa 3474 potilaan ryhmää, jolle samana tarkasteluaikana tehtiin puhdas sepelvaltimoiden ohitusleikkaus. 40 % tämän ikäluokan potilaista oli naisia (24% tätä nuorempien joukossa). Erityisesti haluttiin selvittää tämän potilasmateriaalin pitkäaikais-ennustetta (5v.) ja siihen vaikuttavia riskitekijöitä. Sekä yksimuuttuja-analysissa että regressioanalyysissa todettiin sokeritaudin, sydämen ulkopuolisen valtimo-kovettumataudin, neurologisen häiriön, tuoreen sydäninfarktin ja kriittisen leikkausta edeltävän tilanteen ennustavan myöhäiskuolleisuutta. 30 vuorokauden sairaalakuolleisuus oli tässä materiaalissa 4,7 %, kun se nuoremmassa ikäryhmässä oli 1,3 %. Viiden vuoden kuluttua oli leikatuista potilaista elossa 77 % ja kymmenen vuoden kuluttua 35% (verrattuna 90% ja 76%:iin nuoremman potilasjoukon kohdalla). Kun näitä potilaita verrattiin kohdennettuun nuorempaan potilasmateriaaliin, todettiin vanhusryhmässä korkeampi sairaalakuolleisuus (4,7%/1,3%), mutta sen jälkeen eloonjäämiskäyrät olivat varsin yhdensuuntaiset.

Tiedetään, että pitkä aortan sulkuaika sekä pitkä perfuusioaika ovat sydänleikkaukseen liittyviä riskitekijöitä. Neljännessä työssä etsittiin molempiin liittyvät riskirajat. Molemmat pilkottiin 30 minuutin aikaväleihin ja tutkittiin leikkaukseen liittyvän kuolleisuuden muutosta sulkuajan ja perfuusioajan kasvaessa. Tässä materiaalissa riskin todettiin oleellisesti lisääntyvän, kun aortan sulkuaika ylittää 150 min. ja perfuusioaika 240 min. (suhteutettuna additiiviseen EuroSCOREen ja leikkauksen kompleksisuuteen). On kuitenkin huomattava, että pitkä aortan sulkuaika ja pitkä perfuusioaika eivät automaattisesti merkitse huonoa ennustetta. Selkeä yhteys postoperatiiviseen sairastuvuuteen on kuitenkin olemassa. Erityisen mielenkiintoista on, että pitkä sulkuaika ja perfuusioaika lisäävät haitallisten aivotapahtumien riskiä. Tässä materiaalissa perfuusioajan pituus oli aortan sulkuaikaa vahvempi kuolleisuuden ennustaja.

Euroopassa sydänleikkauksen riskiä arvioidaan tavallisesti v. 1999 luodun EuroSCORE-luokituksen avulla. EuroSCOREn ongelmaksi tiedetään riskin yliarvioiminen matalan riskiryhmän potilaille ja toisaalta riskin aliarvioiminen hyvin korkean riskin potilailla. Alkuperäisessä EuroSCORE-mittarissa muu kuin CABG-toimenpide arvioitiin riskiksi. Siten esim. yksinkertainen aortaläppäleikkaus saa enemmän riskiarvoa kuin useamman suonen ohitusleikkaus. Myöskään monimutkainen useaa sydämen aluetta käsittelevä leikkaus tai potilaan sydämen ulkopuoliset sairaudet eivät saa niille kuuluvaa riskiarvoa. Työssä V mallinnettiin tilastollisen analyysin avulla Vaasan materiaalista uusi mukailtu EuroSCORE (Modified EuroSCORE), joka ennen kaikkea otti paremmin huomioon alentuneen munuaisfunktion vaikutuksen (preoperatiivisen laskennallisen glomerulusfiltraation avulla) ja toisaalta toimenpiteen kompleksisuuden aiheuttaman riskilisäyksen. Työssä VI tämä malli testattiin ja validoitiin Tampereen yliopistosairaalassa tammikuun 2004 ja joulukuun 2008 välisenä aikana leikatun 4014 sydänkirurgisen aikuispotilaan avulla. Mallin todettiin ennustavan toteutunutta kuolleisuutta tarkemmin kuin alkuperäisen EuroSCORE-mittarin. Erityisen mielenkiintoista oli, että malli ennusti kuolleisuutta tarkasti korkean riskin potilaille.

ABBREVIATIONS

ABI	Ankle-brachial index
ACC	American College of Cardiology
ACS	Acute coronary syndrome
AF	Atrial fibrillation
AHA	American Heart Association
AKI	Acute kidney injury
AMI	Acute myocardial infarction
ANOVA	Analysis of variance
AP	Angina pectoris
APACHE	Acute physiology, age, chronic health evaluation
ARF	Acute renal failure
ASO	Arteriosclerosis obliterans
AUC	Area under the receiver operating characteristics curve
AVR	Aortic valve reconstruction
BCP	Blood cardioplegia
BSA	Body surface area
CAD	Coronary artery disease
CAB(G)	Coronary artery bypass (grafting)
CHD	Coronary heart disease
CHF	Congestive heart failure
CI	Confidence interval
C-CPB	Conventional cardiopulmonary bypass
CCP	Crystalloid cardioplegia
CCS	Canadian Cardiovascular Society

CF	Calibration factor
CHD	Coronary heart disease
CK	Creatine kinase
CK-Mb	Creatine kinase MB isoenzyme
COPD	Chronic obstructive pulmonary disease
CPB	Cardiopulmonary bypass
CPBT	Cardiopulmonary bypass time
CRP	C-reactive protein
CVD	Cerebral vascular disease
DW-MRI	Diffusion-weighted magnetic resonance imaging
DM	Diabetes mellitus
ECC	Extracorporeal circulation
ECG	Electrocardiogram
EF	Ejection fraction
EuroSCORE	European system for cardiac operative risk evaluation
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GFR	Glomerular filtration rate
GOLD	Global Strategy for the Diagnosis, Management and Prevention of COPD
HRQoL	Health-related quality of life
IABP	Intra-aortic balloon pump
ICU	Intensive care unit
IMA	Internal mammary artery
IMT	Intima-media thickness
ITA	Internal thoracic artery
LOS	Low output syndrome
LV	Left ventricle
LVEF	Left ventricular ejection fraction
Mini-CPB	Miniaturized cardiopulmonary bypass
MRI	Magnetic resonance imaging
NYHA	New York Heart Association

MACE	Major adverse cardiovascular event
MACCE	Major adverse cardiovascular or cerebral vascular event
MI	Myocardial infarction
NE	Neurologic event
NSTE-ACS	Non ST-segment elevation acute coronary syndrome
NSTEMI	Non ST-segment elevation myocardial infarction
OPCAB	Off-pump coronary artery bypass
OR	Odds ratio
PAD	Peripheral artery disease
PCI	Percutaneous coronary intervention
PVD	Peripheral vascular disease
ROC	Receiver operating characteristic
SIRS	Systemic inflammatory response syndrome
SPSS	Statistical Package for the Social Sciences
SRI	Simplified renal index
STEMI	ST-segment elevation myocardial infarction
STS	Society of Thoracic Surgeons
STS NCD	National adult cardiac surgery database
TAAD	Thoracic aortic aneurysm dissection
TIA	Transient ischemic attack
TIMI	Thrombolysis in myocardial infarction
TORCH	Towards a Revolution in COPD Health
UAP/USA	Unstable angina pectoris
XCT	Aortic cross clamp time

LIST OF ORIGINAL PUBLICATIONS

This dissertation is based on the following original articles, which are referred to in the text by their Roman numerals:

I Nissinen J, Biancari F, Wistbacka JO, Niemi R, Loponen P, Tarkiainen P, Tarkka M. Pulmonary function and immediate outcome of patients undergoing aortic valve replacement. J Heart Valve Dis 2009;18:374–379.

II Nissinen J, Biancari F, Wistbacka JO, Loponen P, Kairi P, Korpilahti K, Tarkka M. Pulmonary function and immediate and late outcome after coronary artery bypass surgery. J Cardiovasc Surg (accepted, in press).

III Nissinen J, Wistbacka JO, Loponen P, Korpilahti K, Teittinen K, Virkkilä M, Tarkka M, Biancari F. Coronary artery bypass surgery in octogenarians: long-term outcome can be better than expected. Ann Thorac Surg 2010;89:1119–1124.

IV Nissinen J, Biancari F, Wistbacka JO, Peltola T, Loponen P, Tarkiainen P, Virkkilä M, Tarkka M. Safe time limits of aortic cross-clamping and cardiopulmonary bypass in adult cardiac surgery. Perfusion 2009;24:297–305.

V Nissinen J, Biancari F, Wistbacka JO, Loponen P, Teittinen K, Tarkiainen P, Koivisto SP, Tarkka M. Is it possible to improve the accuracy of EuroSCORE? Eur J Cardiothorac Surg 2009;36:799–804.

VI Biancari F, Laurikka J, Wistbacka JO, Nissinen J, Tarkka M. External validation of modified EuroSCORE. World Journal of Surgery (accepted, in press)

1 INTRODUCTION

However delicate and sophisticated a cardiac operation is, it still carries a basic risk. This risk depends on the magnitude and complexity of the operation, the characteristics of the patient and the institution the patient is referred to.

Estimating the risk of severe complications associated with a cardiac operation is a fundamental aspect of patient evaluation. More rigorous expectations for obtaining consent and a more enquiring patient population have made risk assessment even more important. Risk evaluation and especially control of risks have important economic and operational implications. Considering the risks to the patient is a meaningful way to plan the operation and the resources required.

Indices and scoring systems designed to estimate risk have been developed over decades. These form the basis for discussions with individual patients when the forthcoming procedures or complications are enumerated. Based on large population studies these scores are usually very accurate in predicting statistical odds for adverse events. – Individually the prognosis of a patient is anyway more uncertain and cannot be determined by a scoring system alone.

Patient populations may differ significantly between institutions and geographic areas. Cardiac surgery is also now performed in an increasingly high-risk population. Aging, co-morbidities, failing ventricles and expanding demands for urgent operations make patient care even more demanding. Crude estimation of mortality rates has only a limited value without knowledge of the patient's risk profile as a whole. Various risk stratification models have been developed to correct for differences between populations and to allow comparison of actual outcome with the predicted outcome. Those models, however, are not all-inclusive and tend to either underestimate or overestimate the individual risk. This is a legacy of their historical nature, generalized structure not being able to consider every meaningful detail and fast development of surgical practice.

The estimate of average perioperative mortality is increasing, since older, sicker and more acute patients are referred to cardiac surgery. However, the hospital mortality has remained unchanged or even slightly reduced because of improvements in medical care. Meanwhile, an increase of postoperative complications has led to an increase of surviving patients with prolonged intensive care unit (ICU) and hospital length of stay with increasing costs, individual suffering and consumption of medical resources. (Warner CD 1997).

Therefore, creating a detailed individual institutional risk profile is worthwhile for more reliable and accurate patient screening. Although this kind of profile merely reflects the results of the particular institution, its predictability and accuracy for individual assessment can be rewarding. Testing and validation of such a profile with materials of similar institutes eliminate any crude biases and are to be recommended.

The aim of the present study was to create a more precise tool for risk estimation by analysing the adult cardiac surgical material operated in the Vaasa Central Hospital from 1994 through 2008. Updating of the EuroSCORE system - currently in the ascendant, at least in Europe – has been one special consideration. More weight was put to the complexity of the procedure, and effort was invested in outlining safety limits for more demanding operations. Particular attention was paid to the evaluation of preoperative pulmonary function, as well as the peri- and postoperative outcome of older people – a growing part of the surgical population.

2 REVIEW OF THE LITERATURE

2.1 The importance of identifying the predictors of outcome

Estimating the risks of serious complications associated with cardiac surgery is a fundamental aspect of both surgery and clinical anaesthesia. As a result of continually improving surgical strategy and the technology which supports it, cardiac surgery is now possible in an increasingly aging and increasingly high-risk population (Warner et al. 1997). In a context of increased control of growing health-care expenditures it is important to assess cardiac surgical results as precisely as possible (Kolh 2006). Given fairly low operative mortality but an increasing number of disturbances from vital organs, more sensitive models predicting forthcoming problems are needed (Warner et al. 1997). The target should be on comparing different methods of treatment and planning optimal sharing of limited resources.

From the patient's standpoint the main goals of preoperative risk assessment are quantification of the individual operative risk and the potential reduction of this risk by various interventions. These interventions may include modifying drug therapy, intensified physical training, individually planned operative procedure, more intensive intraoperative monitoring, anaesthetic and surgical techniques and postoperative care (Kurki 1997). Applying catheter-based techniques for high risk aortic valve operations or giving preoperative levosimendan-infusion to an uncompensated patient with severe heart failure are some examples of attempts to improve the patients' outcome (Eriksson et al 2009). For the patient and his/her relatives, knowledge of the exact calculated risk associated with a certain operation is also of major importance. It must be underlined that risk stratification models score the risks of the patient, but not the quality of care (Kolh,P. 2006).

From a global perspective the interpretation and comparison of published materials requires a uniformly accepted and validated scoring system, according to which presented patients are adjusted.

2.2 Preoperative risk factors

Outcomes of interest in cardiac surgery include mortality, morbidity, major adverse events (i.e. perioperative myocardial infarction, stroke, acute kidney injury), resource utilization, functional postoperative status and patient satisfaction. Independent predictable variables affecting outcome can be categorized as preoperative patient characteristics, type and severity of the cardiac disease, preoperative measurement of physiologic parameters and type and extent of the surgical procedure. Unpredictable variables include intraoperative events with a fundamental impact on postoperative outcome.

2.2.1 Patient characteristics

Patient characteristics are related to individual patients' personal features.

Age

Age is an elementary determinant of outcome, although the relationship between advanced age and poor outcome is neither linear nor consistent from patient to patient (Higgins 1998). Traditionally, the age of 65 years has been used as a cutoff value differentiating between elderly and younger patients. With the improvement in the general health of the population and in medical care, no particular cutoff age may any longer be valid as an exclusion criterion. However, mortality rises steadily after the age of 60 years (Higgins et al. 1992c, Roques et al. 1999). Figure 1 shows the influence of age on mortality according to logistic EuroSCORE. Patients are divided into cohorts at intervals of five years. According to the logistic EuroSCORE, mortality below age 60 is calculated to be 0.88 %. At age 60 it is 0.93 % and rises progressively to be almost tenfold at the age of 95.

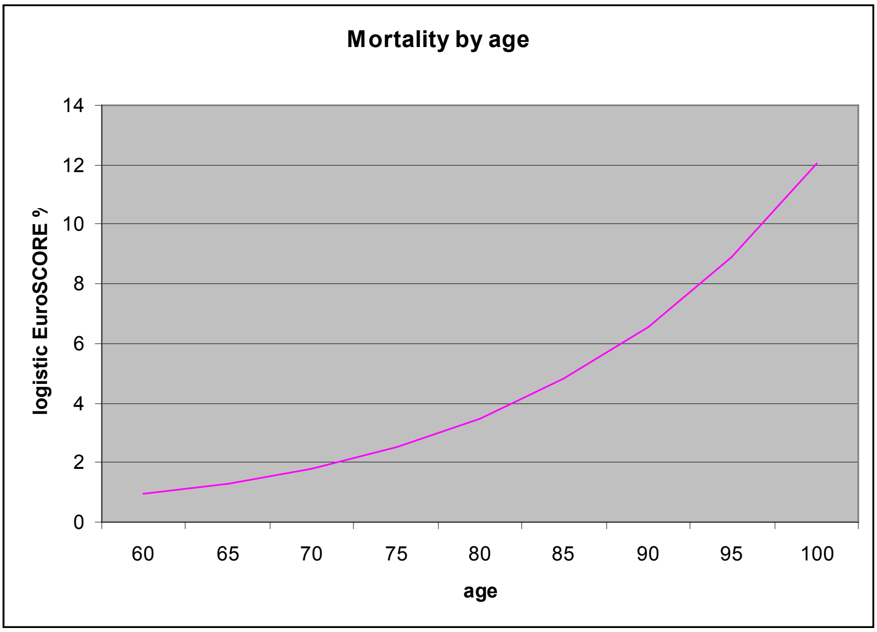


Figure 1. Influence of age on mortality according to the logistic EuroSCORE.

Sex

Many studies quote female sex as a risk factor for both mortality and morbidity (O'Connor et al. 1993b) and this variable is included in most cardiac surgery risk scoring methods (Parsonnet et al. 1989, Edwards et al. 1994b, Roques et al. 1999). Tan et al. in their review show that the higher prevalence of hypertension, diabetes and obesity in older women portends a greater risk in women than in men (Tan et al. 2010). Although cardiovascular mortality for men has been declining, the number of women dying from cardiovascular disease has slightly increased (Tremmel and Yeung 2007). Female patients referred to CABG are often older and have several co-morbidities (Koch et al. 1996) such as higher age, hypertension, diabetes or metabolic syndrome, heart failure, renal disease, peripheral vascular disease, and worse lipid profile (Dullum and Dullum 2008). Additionally, risk factors like smoking, hypertriglyseridemia and low high-density lipoprotein cholesterol levels have greater impact in women than in men (Tan et al. 2010). Hogue also showed that women undergoing cardiac surgery have a higher incidence of periprocedural morbid events, such as stroke and bleeding, compared with men (Hogue et al. 2001).

Some studies have examined both sex and body size in the same population and noted that it is rather small body size and not sex that increases risk in female gender. (Fisher et al. 1982, Parsonnet et al. 1989, Higgins et al. 1992b, O'Connor et al. 1993b). The clinical picture of women's heart disease is variable, possibly resulting in delays in diagnosis and treatment. In comparison to men women also more often have unstable angina, as well as severe angina and congestive heart failure (Jacobs 2003). Congestive heart failure has been shown to account for excess mortality in women undergoing coronary artery bypass grafting (CABG) (O'Connor et al. 1993a).

Increased mortality of women in CABG surgery may also be due to referral bias. Women are referred for coronary bypass surgery later in the course of their disease than men, hence being older than men, having a higher percentage of unstable angina pectoris, postmyocardial infarction angina, congestive heart failure, and New York Heart Association class IV symptoms (Khan et al. 1990).

There has been general acceptance that women undergoing bypass surgery have a mortality double that of their male peers and mortality rates as high as 4 times that of men have been reported in women following CABG (Hogue, C.W.,Jr 2001, Vaccarino et al. 2002). Recent sex-based analysis has suggested that diabetes and urgency or emergency presentation accounts for this manifold mortality risk (Wenger 2003). This is especially true in younger age groups. In a National Cardiovascular Network database survey from 1993 to 1999 the odds ratio for post-CABG in-hospital mortality for patients <50 years of age was 2.23 for women compared with men. This difference decreased with age, and disappeared for patients >80 years of age (Vaccarino et al. 2002).

Some recent studies by Blankstein and Tan confirm that female gender is an independent predictor of perioperative mortality, even after accounting for all comorbidities, and including low body surface area, BSA (Women 4.24% versus men 2.23%) (Blankstein et al. 2005). However, after discharge from hospital, adjusted survival at 5 years after CABG seems to be similar in women and men (Herlitz et al. 2000).

Body size

Obese people carry a higher statistical risk of death (Manson et al. 1995, Solomon and Manson 1997, Gelber et al. 2007). At least three studies have confirmed the risk of morbid obesity in patients undergoing cardiac surgery. Paiement in the Montreal Heart Classification found body mass index over 0.30 to be an independent risk factor (Paiement,B. 1983). Parsonnet in his risk model defined morbid obesity as at least 1.5 times normal weight. The logistic coefficient for overweight was -0.271 with a p-value of 0.027 (Parsonnet et al. 1989). Prasad et al.found no difference in perioperative mortality, but respiratory problems ($p< 0.01$); leg wound infections ($p< 0.001$); myocardial infarction ($p< 0.02$); arrhythmias ($p< 0.02$); and sternal wound dehiscence ($p< 0.02$) were more common in obese patients (Prasad et al. 1991). At a mean follow-up time of 36.9 months obese patients exhibited a greater incidence of significant recurrent angina ($p < 0.01$), which was associated with further weight gain (mean 12.2 kg; linear correlation: $p< 0.001$, $r = 0.891$). Higgins in the Cleveland Clinic model found a bodyweight < 65 kg to be a risk factor (Higgins 1998). Newer risk models used nowadays (EuroSCORE and STS) have not found overweight to be an independent risk factor.

Heredity

Clinicians tend to consider family history of CHD when evaluating CHD risk. However, quantitative methods taking into account family history of CHD are not readily available. Nor does any risk model identify heredity as a measured variable. The genetic background of some cardiovascular disorders, however, is well known. For example, thoracic aortic aneurysms leading to type A dissections (TAAD) may occur in isolation or in association with genetic syndromes, such as Marfan syndrome or Loeys-Dietz syndrome. Familial TAAD is inherited in an autosomal dominant manner with decreased penetrance (especially in women) and variable expression and exhibits significant clinical and genetic heterogeneity (Collod-Beroud et al. 1997, Pearson GD. Devereux R. Loeys B. Maslen C. Milewicz D. Pyeritz R. Ramirez F. Rifkin D. Sakai L. Svensson L. Wessels A. Van Eyk J. Dietz HC. National Heart, Lung and Blood Institute and National Marfan Foundation Working Group 2008). Bicuspid aortic valve (BAV) with its co-morbidities also seems to be highly heritable. In a study by Cripe, where a total of 309 probands and relatives participated in an investigaton of the heritability of BAV and BAV and/or other cardiovascular malformations, the heritability figures were 89% and 75% respectively (Cripe et al. 2004).

2.2.2 Comorbidities

Chronic pulmonary disease

Pulmonary disease defined according to EuroSCORE criteria provides long term use of bronchodilators or steroids for lung disease. Severity of COPD is classified according to the Global Strategy for the Diagnosis, Management and Prevention of COPD (GOLD) (Rabe et al. 2007)

Table 1. GOLD Staging System for COPD Severity

Stage	Description	Findings (based on postbronchodilator FEV1)
0	At risk	Risk factors and chronic symptoms but normal spirometry
I	Mild	FEV1/FVC ratio less than 70 percent FEV1 at least 80 percent of predicted value May have symptoms
II	Moderate	FEV1/FVC ratio less than 70 percent FEV1 50 percent to less than 80 percent of predicted value May have chronic symptoms
III	Severe	FEV1/FVC ratio less than 70 percent FEV1 30 percent to less than 50 percent of predicted value May have chronic symptoms
IV	Very severe	FEV1/FVC ratio less than 70 percent FEV1 less than 30 percent of predicted value or FEV1 less than 50 percent of predicted value plus severe chronic symptoms

GOLD = Global Initiative for Chronic Obstructive Lung Disease; COPD = chronic obstructive pulmonary disease; FEV1 = forced expiratory volume in one second; FVC = forced vital capacity.

Patients with severe chronic obstructive pulmonary disease (COPD) are known to be at increased risk of mortality and morbidity (Ranieri et al. 2008). This is particularly true when they undergo major surgery (Kroenke et al. 1992). A few risk scoring methods include pulmonary disease as a major determinant of mortality after adult cardiac surgery (Higgins et al. 1992a, Magovern et al. 1996, Roques et al. 1999). On the other hand, the adverse role of this condition has not been recognized in several other major risk scoring methods (Parsonnet et al. 1989, Grover et al. 1993, Ivanov et al. 1999, Huijskes et al. 2003). COPD has earlier been shown to predict the immediate outcome after coronary artery bypass surgery (Samuels et al. 1998a, Fuster et al. 2006) and after aortic valve reconstruction (AVR) , although a recent review by Tjang failed to identify pulmonary disease as a risk factor for early mortality of AVR (Tjang et al. 2007). Angouras et al. found similar results in their study, where 3,760 CABG patients were followed up for 7.6 years (mean). Of these 14.6% had COPD. COPD-patients were older and sicker. When compared to propensity-matched patients without COPD, no difference was noted in terms of hospital mortality or major morbidity. By contrast, COPD-patients had increased long-term mortality with a hazard ratio of 1.28 (95% confidence intervals, 1.11 to 1.47; $p = 0.001$) (Angouras,D.C. 2010).

Extracardiac arteriopathy

The extent and severity of atherosclerotic lesions in major and peripheral arteries correlate with the extent and severity of coronary artery disease (Amanullah et al. 2002, Sukhija et al. 2003, Rohani et al. 2005, Lekakis et al. 2005). Among patients undergoing major surgery for peripheral artery disease (PAD), the prevalence of CAD ranges from 25% to 78%, and myocardial infarction is the main cause of perioperative death (Monaco et al. 2009). In Hertzer's study, severe correctable CAD was identified in 25% of the entire series of 1,000 patients under consideration for elective peripheral vascular reconstruction (Hertzer et al. 1984).

The European system for cardiac operative risk evaluation (EuroSCORE) considers extracardiac arteriopathy as a risk factor for early mortality. In a recent study from Netherlands and Belgium 10,626 patients underwent isolated coronary artery bypass operation in a 10-year period. Out of these patients 1,222 (11.6%)

had peripheral vascular disease (PVD). The PVD was identified as an independent risk factor for late mortality (death at any time after hospital discharge), but not for early mortality (death within 30 days or before discharge). Patients without PVD had a better survival than patients with PVD: 2.3%/3.6% early mortality and 10,1%/19.1% late mortality ($p<0.0001$), respectively (van Straten et al. 2010).

Symptomatic carotid disease increases the risk of stroke, and the management of patients with both symptomatic coronary and carotid artery diseases demands careful consideration (Wong 1991). In St.Louis, 1,087 patients 65 years of age and older undergoing cardiac surgical procedures (91% had coronary artery disease) were evaluated before operation with carotid duplex ultrasonography. The prevalence of disease was 17.0% for 50% or greater stenosis and 5.9% for 80% or greater stenosis (Berens,E.S. 1992). Hill in 2000 stated that asymptomatic unilateral carotid stenosis of 80–90% appears to be independently associated with ipsilateral hemispheric stroke following cardiac surgery and increases the risk of stroke 5.2 fold (Hill,A.B. 2000). Ascher 2001 recommended carotid screening for patients under 60 years only in the presence of two of the following risk factors: hypertension, diabetes or smoking. However, carotid screening is recommended for all patients undergoing open heart operations who are more than 60 years old (Ascher et al. 2001). On the other hand Archbold et al. recommended screening for all patients with a history of stroke or TIA, all patients with a carotid bruit, and all patients aged > 65 years (Archbold,R.A. 2001). It is suggested that prophylactic carotid endarterectomy could neutralize the risk in those with at least 80% carotid stenosis (Gott,J.P. 1999). In a preoperative MRI-study by Goto on 421 elderly people, it was observed that 30% of patients had small brain infarctions and 20% had multiple infarctions (Goto et al. 2001). These findings of the extent of cerebrovascular disease were correlated with the occurrence of both postoperative stroke (1.4%/5.6%/8.4%) and cognitive change (7%/13%/20%) in control/ small infarct/ multiple infarct groups consecutively. In another Japanese study including a combination of MRI and magnetic resonance angiography, an even higher prevalence of cerebrovascular disease was found preoperatively in 39 CABG patients. Existing cerebral infarction was found in 97%, internal carotid artery disease in 25%, periventricular hyperintensities in 87% and external carotid artery disease in

41% (Nakamura et al. 2004). Thus it may be important to consider investigating the carotid arteries before a cardiac operation. On the other hand, meta-analyses questioned the value of carotid revascularization in patients undergoing CABG as the combined approach is associated with rather high risk of stroke/death (Borger and Fremes 2001, Naylor et al. 2009).

Neurological dysfunction

Stroke remains a devastating complication after cardiac surgical procedures. In addition to several known risk factors for postoperative neurologic events (NE), a history of preoperative NEs has also been reported to be associated with an increased risk of postoperative NEs (Rorick and Furlan 1990, Tuman et al. 1992, Mickleborough et al. 1996, Redmond et al. 1996, Halkos et al. 2008). In the study by Halkos a total of 14,278 patients prospectively registered were retrospectively analysed, 1,478 patients (10.4 %) having a history of preoperative NEs. Postoperative neurological events occurred in 1.9% (274 patients). In a propensity score matched analysis it was found that patients with preoperative NEs had three times more postoperative NEs than a matched cohort (4.6% vs. 1.6%; $p<0.0001$). Patients with preoperative NEs also had longer duration of postoperative ventilation and longer hospital stays.

In other studies, evaluating the effect of preoperative NEs in patients operated using cardiopulmonary bypass, Redmond et al. documented a 44% stroke incidence and Rorick and Furlan reported a 13% stroke incidence postoperatively (Rorick and Furlan 1990, Redmond et al. 1996). In a large study by Bucerius ($n=16,184$), a previous history of cerebrovascular disease was a significant risk (OR 3.55) for postoperative stroke (Bucerius et al. 2003a). This and other studies (Anyanwu et al. 2007) also showed that those patients with stroke had 6-fold higher mortality (32.8% versus 4.9%, $p<0.0001$). Dacey et al. in the Northern New England Cardiovascular Disease Study Group showed that those patients postoperatively diagnosed with stroke had a three-fold greater risk of death during 10-year follow-up (Dacey et al. 2005). Other authors also observed that a prior neurological event was an independent predictor for both early and late postoperative stroke (Hogue et al. 1999, Anyanwu et al. 2007).

Postoperative neurologic disturbances

It seems likely that patients with postoperative coma, stroke and encephalopathy represent a continuum of conditions with similar underlying mechanisms: showers of embolic material to the brain, whether they then are gaseous or particular (Gootjes et al. 2005). Encephalopathy is a diffuse brain injury with clinical manifestations including confusion, delirium, seizures, comatose state of consciousness, prolonged state of mental alteration, aggressiveness and agitation. Its reported incidence varies widely from 8.4% to 32% depending on difficulties in getting this condition formally diagnosed (McKhann et al. 2006). Like stroke, encephalopathy is also associated with increased length of stay in the hospital, and with 3 times higher mortality than in patients without this complication. The factors that appeared important were history of previous stroke, hypertension, diabetes, presence of carotid bruit, and age.

Patients operated off-pump were likely to have a reduced risk of postoperative NEs compared to patients operated on-pump (Wijeysundera, D.N. 2005, Biancari,F. 2007). However, OPCAB does not confer additional risk reduction in patients with preoperative neurological events. Friday in a prospective diffusion-weighted magnetic resonance imaging (DW-MRI) found that ischaemic lesions at DW-MRI are seen after off-pump CABG at a rate similar to that reported for CABG with cardiopulmonary bypass (Friday,G. 2005). Lund in his prospective randomized study found a reduction in the number of microemboli measured by transcranial doppler during off-pump compared with on-pump surgery (16.3 [range 0 to 131] versus 90.0 [range 15 to 274], $p < 0.0001$). However, no significant difference was found with regard to the incidence of neuropsychologic performance (decline in 29% off-pump, 35% on-pump) or neuroradiologic findings at 3 months, and there was no association between the number of cerebral microemboli and cognitive outcome (Lund,C. 2003).

The incidence of stroke is much higher in the setting of combined cardiac procedures (> 2) and in more technically challenging operations, such as aortic aneurysm repairs with the use of hypothermic circulatory arrest or in conjunction with extended perfusion times (Anyanwu et al. 2007).

Renal failure

Renal dysfunction following cardiac surgery is well recognised as being mainly of ischaemic origin, but its precise pathogenesis is complex and multifactorial. It likely involves at least six major injury pathways: exogenous and endogenous toxins, metabolic factors, ischaemia and reperfusion, neurohormonal activation, inflammation and oxidative stress (Bellomo et al. 2004). The spectrum varies from subclinical injury to established renal failure requiring renal replacement therapy. Depending on definitions, acute kidney injury (AKI) after cardiac surgery generally occurs in 1–10% of patients (Mehta 2005) but may occur in up to 30% of post-cardiac surgery patients (Vaschetto and Groeneveld 2007). Dialysis is required in approximately 1%–2% of all patients (Ostermann, M.E. 2000. Rosner and Okusa 2006). Mortality rates associated with perioperative acute renal failure range from 60% to 90% (Sheinbaum et al. 2003). Even small decreases in kidney function are associated with poorer outcome. The risk of death associated with AKI after cardiothoracic surgery remains high for 10 years regardless of other risk factors, even for those patients with complete renal recovery (an increased adjusted hazard ratio for death of 1.28) (Hobson et al. 2009). Several clinical studies have identified risk factors that can be used to effectively determine the risk for AKI in patients undergoing cardiac surgery. The Consensus Conference of the Acute Dialysis Quality Initiative in 2004 suggested a consensus definition named RIFLE (Risk of renal dysfunction; Injury to the kidney; Failure of kidney function; Loss of kidney function; and End-stage kidney disease) attempting to get uniform and generally accepted criteria for acute renal failure (ARF). However, its impact on surgical practice seems to be of minor importance. Wijeysundera et al. in 2007 derived and validated the Simplified Renal Index (SRI) for estimating the risk of renal replacement therapy after cardiac surgery (Wijeysundera et al. 2007).

Table 2. The Simplified Renal Index (SRI) risk factors.

Variables	Points
Estimated GFR 31–60 ml/min	1
Estimated GFR <30 ml/min	2
Diabetes mellitus requiring medication	1
Left ventricular ejection fraction <40%	1
Previous cardiac surgery	1
Procedures other than CABG or atrial septal repair	1
Nonelective procedure	1
Preoperative intra-aortic balloon pump	1

GFR, glomerular filtration rate, derived from Cockroft and Gault, 1976

Eight predictors of the need for replacement therapy were identified. A minority of patients (6%) had high risk scores (> 4) translating into a 10% risk of requiring replacement therapy (Wijeysundera et al. 2007). As can be seen, most risk factors included in SRI are also included in usual cardiac surgery risk models. There is no uniform consensus on what level of renal function should be labelled as evidence of pre-existing renal insufficiency.

In a recent German study 2,522 consecutive patients (men age 69$\pm$12 years, 68% male) underwent cardiac surgery between years 2007–2009. Renal failure requiring dialysis occurred in 3.9% (n=98) of patients. Hospital mortality among them was 37.8% compared to a mortality rate of 1.3% in patients without this complication. Multivariate analysis revealed pulmonary hypertension (OR=8.1), preoperative renal dysfunction (creatinine >2.0 mg/dl)(OR=4.6), cardiopulmonary bypass time >120 min. (OR=3.9), peripheral vascular disease (OR=3.1), previous myocardial infarction (OR=3.0), atrial fibrillation (OR=2.8), age >75 years (OR=2.6), New York Heart Association class IV (OR=2.5) and diabetes (OR=2.0) as independent predictors for postoperative AKI (Rahmanian 2010).

The only parameter incorporated into the cardiac surgery models of today is serum creatinine, in spite of the fact that neither serum creatinine nor creatinine clearance will accurately reflect the GFR in the non-steady-state condition of acute renal failure. Nonetheless, the degree to which serum creatinine changes from baseline also reflects the change in GFR (Bellomo et al. 2004). The superiority of estimated glomerular filtration rate (eGFR) over serum creatinine as a measure of renal function has recently been claimed (Stevens et al. 2006). EGFR has a major impact as a predictive tool of subclinical degrees of renal failure on the immediate and late outcome of patients undergoing CABG (Kangasniemi et al. 2008). Comparing eGFR to serum creatinine (eGFR <60 ml/min/1.73m^2 vs. serum creatinine >150 mg/dl or >200 mg/dl), eGFR was the only significant predictor of 30-day postoperative mortality. In this study, poor late overall survival during a 10-year follow-up was also particularly evident among patients with eGFR <60ml/min/1.73m^2.

In a meta-analysis of randomized and observational studies on off-pump CABG and AKI Nigwekar et al. stated that a significant reduction in overall AKI and renal replacement therapy was achieved in the OPCAB group compared with the CABG group (Nigwekar et al. 2009).

Current strategies to provide perioperative renal protection include maintaining adequate renal O2 delivery, suppressing renovascular vasoconstriction, maintaining renovascular vasodilatation and tubular flow, decreasing renal cellular O2 consumption, and attenuating reperfusion injury (Sheinbaum et al. 2003). Palombaet al. in 2007 published the Acute Kidney Injury after Cardiac Surgery (AKICS) score based on a single Brazilian centre cohort of patients who underwent elective cardiac surgery. Both pre- intra- and postoperative variables were incorporated in the risk model developing AKI not requiring dialysis after cardiac surgery. Here cardiopulmonary bypass time of more than 120 min and a postoperative central venous pressure of higher than 14 cmH2O were found to be significant risk factors for AKI after cardiac surgery.

Diabetes mellitus

The importance of diabetes mellitus (DM) as a cause of mortality and morbidity is well known (Feskens and Kromhout 1992, Gol et al. 1998). DM type II is preceded by longstanding asymptomatic hyperglycaemia, which accounts for the development of long-term diabetic complications. The connection was demonstrated in a prospective study on elderly Finnish people, whose risk of fatal and nonfatal cardiovascular events after 3.5 years was greater than 4-fold in the presence of diabetes than in its absence (Kuusisto et al. 1994).

Diabetes mellitus is as much a vascular disease as it is a metabolic disorder. The main macrovascular complications, for which diabetes has been a well established risk factor throughout the cardiovascular system, are: coronary artery disease (CAD), peripheral vascular disease (PVD), increased intima-media thickness (IMT) and stroke. Diabetics have a 2 to 4-fold increased risk of CAD (Feskens and Kromhout 1992). Cardiovascular disease (CVD) is the cause of death in 65 % of patients with diabetes, whereas only 35 % of deaths in non-diabetic persons can be attributed to CVD (Yosefy 2008). Using coronary angiography as the diagnostic tool multivessel disease was found to be more common in diabetics than in controls, with three-vessel disease being the most common (Fallow and Singh 2004). Diabetic patients were also more likely to have more segments diseased in one vessel. Systolic function was impaired in the diabetic group with lower mean ejection fraction ($p<0.05$). This study corroborates the evidence that diabetic patients have more extensive coronary artery disease than non-diabetics and a poorer prognosis. This is also demonstrated by the OASIS and GUSTO II trials, where diabetic patients with acute coronary syndrome are still at substantial risk of increased mortality and morbidity (Malmberg et al. 2000, McGuire et al. 2000).

Impaired renal function as a result of nephropathy and neuropathy, particularly that involving the autonomic nervous system are other ramifications of DM, impairing the likelihood of a diabetic patient withstanding major surgery. Moreover, diabetes is a well-established independent risk factor for stroke.

Hyperglycaemia is a normal response to stress. Normally, insulin release is stimulated by elevated levels of glucose. When glucose levels fall, the counter-regulatory hormones (adrenaline,glucagon, growth hormone, and cortisol) facilitate glycolysis, releasing glucose from hepatic stores and promoting gluconeogenesis in peripheral tissues. During times of stress, such as surgery, there is an increase in the levels of counter-regulatory hormones and inflammatory cytokines, such as tumor necrosis factor and interleukins, which results in increased hepatic glucose production, impaired peripheral glucose utilization, relative insulin deficiency, and hyperglycaemia (Shine et al. 2007). In a critically ill patient or during surgery, hyperglycaemia may be detrimental. Treating hyperglycaemia in the operating theatre or ICU is complicated by the fact that many cardiac surgical patients have insulin resistance (Macheda et al. 2005).

Considering the cardiovascular surgery, DM is associated with an increased rate of early and late complications following cardiac surgery (Yosefy 2008). In 2005, Gandhi et al. at the Mayo clinic reported on 409 patients undergoing cardiac surgery and found that intraoperative hyperglycaemia was associated with postoperative mortality and morbidity. When the blood glucose concentration was >5.55 mmol/l (100 mg/dl), a 1.11 mmol/l (20 mg/dl) increase in glucose concentration was associated with a 34% increase in the number of postoperative adverse events (Gandhi et al. 2005). Surgical site infections (SSI) are among the most feared complications among all cardiac surgery patients. Several studies have shown diabetes and postoperative hyperglycaemia to be important causative risk factors for postoperative SSI (Gol et al. 1998, Latham et al. 2001). Individuals with type 2 DM are at higher risk for postoperative infections due to a muted immune response, the effects of hyperglycaemia on neutrophil function and pathogen proliferation, and the negative effects of impaired tissue perfusion. Hyperglycaemia resulting from insulin resistance is common in critically ill patients, including those who have not previously been diagnosed with diabetes. Factors contributing to postoperative hyperglycaemia include increased levels of catecholamines, growth hormone, and corticosteroids. Higher glucose levels may also result from pharmacologic agents commonly used during and following surgery, such as heparin and beta-blockers (Patel 2008). Up to 6 % of patients with no prior history of diabetes may have evidence of undiagnosed diabetes. Their infection rate seems to be comparable to that of known diabetics (Latham et al. 2001).

Liver cirrhosis

Cardiac surgery is seldom performed on patients with liver cirrhosis and its outcome has been reported only in small series (Klemperer MD et al. 1998, Bizouarn et al. 1999, Kaplan et al. 2002, Hayashida et al. 2004). Cardiac operations may be performed with good results for patients suffering from liver disease of mild severity (Child A), but cardiac interventions that include CPB in conjunction with advanced hepatic pathologies are associated with high mortality and morbidity (Kaplan et al. 2002). Cirrhosis is not included in usual risk scoring systems.

Other emerging risk factors

Traditional risk factors do not explain all of the risk for incidental heart disease. Various new or emerging risk factors may have the potential to improve global risk assessment for heart disease, especially for coronary heart disease (CHD). Helfand in his survey summarized 9 systematic reviews of novel risk factors to evaluate their clinical usefulness (Helfand et al. 2009). Risk factors analysed were C-reactive protein (CRP), calcium content of the coronary arteries (CAC-score), lipoprotein(a), homocystein, leukocyte count, fasting glucose concentration, periodontal disease, ankle-brachial index (ABI) and carotid intima and media thickness (IMT). Of the 9 markers evaluated, only CRP showed strength of evidence, shown also earlier by Biancari et al. (Biancari et al. 2003). High CRP level may identify a high-risk subset of patients with a Framingham risk score between 15% and 20%. On the other hand CRP count is very nonspecific and manoeuvres like weight loss, smoking cessation, statins and fibrates reduce serum CRP levels. However, none of these effects has yet been linked to a reduced risk for major CHD events.

Low preoperative hematocrit (Higgins et al. 1992b) and albumin levels (Higgins et al. 1997) have also been identified as risk factors, often reflecting chronic illness.

2.2.3 Severity of the cardiac disease

Acute coronary syndromes (ACS)

The term acute coronary syndrome refers to any group of clinical symptoms compatible with acute myocardial ischaemia and includes unstable angina (UAP), non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI) (Iqbal,M.B. 2008). These conditions are associated with high morbidity and mortality. They constitute the most frequent cause of hospital admission related to cardiac disease (Wenaweser and Windecker 2008). Certain patient types require very limited consideration in terms of stratifying their risks; these include those with cardiogenic shock, severe LV dysfunction, persistent severe ischaemia, or malignant arrhythmias, despite maximal medical management.

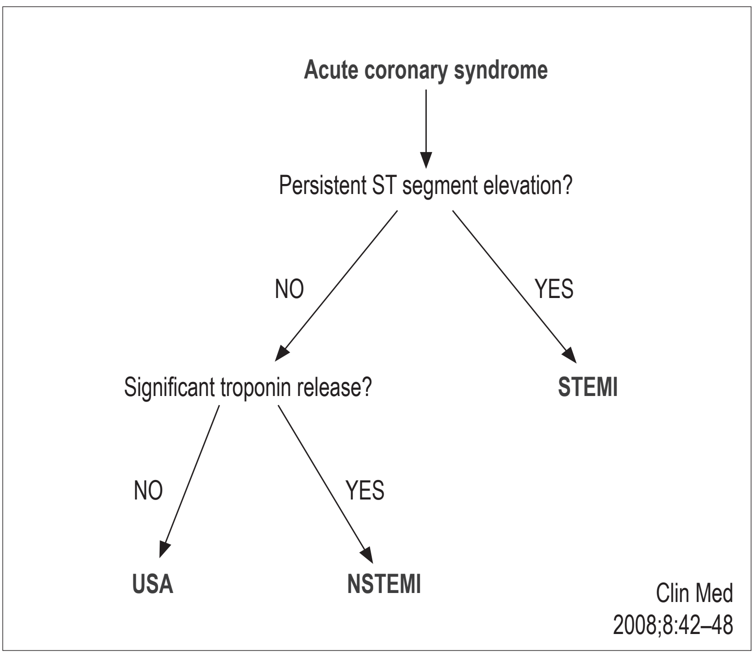


Figure 2. Acute coronary syndromes. (USA: Unstable angina)
Modified from Iqbal et al.

Among patients with unstable angina or non-Q-wave myocardial infarction, there is an increased risk of death within 6 weeks in those with elevated troponin levels and the risk of death continues to increase as the troponin level increases. Reversible ST-segment depression is associated with an increase by a factor of 3–6 in the likelihood of death, myocardial infarction, ischaemia at rest, or provocable ischaemia during a test to stratify risk. Early diagnosis and risk stratification are essential for urgent initiation of optimal medical and invasive treatment.

Risk Stratification Methods

The TIMI (Thrombolysis in Myocardial Infarction) risk score

Table 3. TIMI Risk Score variables

Characteristics	Point
History	
Age >65 years	1
Presence of at least 3 risk factors for CHD	1
Prior coronary stenosis equal or greater than 50%	1
Use of aspirin in prior seven days	1
Presentation	
At least two anginal episodes in previous 24 hours	1
Presence of ST segment elevation on admission ECG	1
Elevated serum markers	1
Risk total score	(0–7)

TIMI scoring was set up to predict 30-day mortality at patient presentation of patients with either STEMI or NSTEMI/UAP (Morrow 2000, Elliott 2000). TIMI scoring uses the seven variables seen in Table 3. The variables are independently predictive for adverse outcome in patients with UAP or NSTEMI (Antman et al.

2000). The TIMI-score may be useful not only for identifying those patients at risk for ischemic complications but also in guiding to specific interventions for ACS.

The baseline ECG

New or reversible ST segment depression greater than 0.5 mm, transient ST elevation or new left bundle branch block are important prognostic signs revealing ACS (Cannon et al. 1997). Although specific for identifying ACS patients, ECG is less sensitive and has poor predictive value; thus a negative ECG does not offer reassurance.

Serum troponins

Serum troponins are now considered the 'gold standard' for the diagnosis of cardiac injury and are useful for quantitative risk stratification in ACS. The troponins are highly cardiac specific, and more sensitive than previously used cardiac markers, such as serum creatine kinase MB-isoenzyme (CK-MB) (Ohman et al. 1996). Because detectable levels of troponin are not present in the blood of patients with NSTEMI until 4–6 hours after myocardial injury, serial blood testing is essential in patients with non-diagnostic ECG but high suspicion of ACS.

Mechanism of ACS

Disruption of vulnerable or high-risk plaques is the common pathophysiological mechanism of acute coronary syndromes with or without ST-elevation (Ross 1999). The great majority of these lesions have proved to be previously angiographically nonsevere with the culprit lesion in up to 80% of patients being less than 70% in severity (Roe et al. 2000). The reflection of the same pathophysiological mechanism differs in non-ST-elevation acute coronary syndromes and ST-elevation myocardial infarction (STEMI) in terms of clinical presentation, prognosis and therapeutic approaches.

Clinical evaluation

For the patient with suspected or proven ACS, the goals for the clinician are to establish a diagnosis, stratify risk and choose optimal therapeutic interventions.

To achieve the goals of risk assessment, several tools are available, including history, physical examination, ECG, serum troponin and various protocols for risk stratification. For high-risk ACS patients with high TIMI-scores, ST-segment depression on ECG, or elevated serum troponins, the urgency is to move toward revascularization procedures in a timely fashion. Standard medical therapies are indicated according to the valid recommendations. For low-risk patients with low TIMI score, negative troponins and no ST depression on ECG, the optimal therapeutic protocol includes optimal medical therapies, stabilization of the patient and noninvasive stress testing before discharge, if recurrent ischaemia does not occur.

It is anticipated that contemporary antiplatelet (aspirin, clopidogrel, prasugrel, ticagrelor, GP IIb/IIIa receptor inhibitors) and anticoagulant therapy lower the risk of peri-interventional ischaemic complications and thereafter an invasive strategy is advised within 24–72 hours of admission in case of ACS (Anderson JL. et al. ACC/AHA Task Force on Practice Guidelines for the Management of Patients With Unstable Angina/Non ST-Elevation Myocardial Infarction. American College of Emergency Physicians. Society for Cardiovascular Angiography and Interventions. Society of Thoracic Surgeons. American Association of Cardiovascular and Pulmonary Rehabilitation. Society for Academic Emergency Medicine 2007). The greatest benefit (<50% relative risk reduction) of an early invasive strategy is observed in moderate to high-risk patients, notably patients with ST segment depression and/or positive troponin test (Wenaweser and Windecker 2008). The current practice guidelines therefore recommend an early invasive strategy consisting of coronary angiography followed by appropriate revascularization by either PCI or CABG as routine management in intermediate to high-risk NSTE-ACS patients. In addition, an urgent invasive strategy should be entertained in patients with severe, ongoing chest pain, dynamic ST segment changes, severe arrhytmias, and haemodynamic instability (Braunwald et al. 2002, ESC guidelines 2010).

However, bleeding is a common complication resulting from administration of these adjunctive powerful drugs and is a serious threat during an urgent operation. The importance of bleeding as a major independent predictor of recurrent myocardial infarction, stroke, and death has been recognized recently in patients with acute coronary syndromes (Eikelboom et al. 2006). Bleeding is likely in patients with high levels of co-morbidity, such as elderly patients or those with chronic kidney disease, who already inherently carry a higher risk. Bleeding may also induce a prothrombotic state as a result of increased concentrations of circulating erythropoietin (Smith et al. 2003). Moreover, blood transfusions can induce a proinflammatory and prothrombotic state (Reeves and Murphy 2008, Budaj et al. 2009,). One could anticipate that reduction in early bleeding can lead to substantial improvements in major adverse clinical events in patients with ACS.

Although the conditions of the majority of patients with low-risk unstable angina will stabilize with effective anti-ischaemic medications, approximately 50–60% of such patients will require coronary angiography and revascularization because of the "failure" of medical therapy. High-risk patients are those who have had angina at rest, prolonged angina, or persistent angina with dynamic ST segment changes or hemodynamic instability (Auer et al. 2001).

Features of high risk according to ACC/AHA guidelines (USA) and European Society of Cardiology Task Force Report (EU), respectively, are seen in Table 4 (Hamm et al. 2001).

Table 4. Features of high risk in connection with acute coronary syndromes in ACC/AHA guidelines (USA) and European Society of Cardiology Task Force Report (EU).

Increased troponin concentrations	EU/USA
Recurrent ischaemia (ST depression, transient ST elevation)	EU/USA
Haemodynamic instability	EU/USA
Major arrhythmias (ventricular tachycardia/ fibrillation)	EU/USA
Early post-infarction angina	EU
High-risk finding on non-invasive stress testing	USA
Depressed left ventricular function (EF <40%)	USA
PCI within 6 months	USA
Previous CABG	USA

(Hamm et al. 2001).

Significant coronary artery lesions are present in 80–90% of patients with ACS. Data from the TACTICS-TIMI 18 trial revealed narrowing of the left main coronary artery in 9%, single vessel disease in 26%, and three-vessel disease in 34% of patients (Weintraub et al. 1999).

Left ventricular function

The available evidence suggests that patients with moderate to severe left ventricular systolic dysfunction and concomitant limiting angina have improved survival with CABG (Alderman et al. 1983). However, both low ejection fraction and clinical heart failure are predictive of higher operative mortality rates with CABG. In early reports including the CASS study, the mortality rate ranged from 18% to 33% (Baker et al.). Still in 1982, left ventricular ejection fraction was considered the most important predictor of perioperative mortality for CABG. By 1986, improved perioperative and surgical techniques had reduced this to the fourth most important predictor, after repeat CABG, urgent surgery, and age (Christakis et al. 1989). In 1993 Elefteriades et al. published a series of patients with a left ventricular ejection fraction < 30% who underwent isolated coronary artery bypass grafting. The hospital mortality rate was 8.4% (Elefteriades et al. 1993). In her article concerning influence of left ventricular function on survival after coronary artery bypass grafting Elisabeth Ståhle, in a material of 6,514 patients, showed that reduced LV function (moderate LV dysfunction, OR 1.4 ; severe LV dysfunction, OR 2.1) was independently related to early mortality giving a 6.6% operative mortality in patients with an EF<35% in contrast to 2.6% in those with an EF>50% (Stahle et al. 1997).

In a prospective study of 426 consecutive patients undergoing cardiac surgery, Atoui et al. observed that EF <40%, high Parsonnet risk score, history of renal failure and emergency surgery were independent risk factors for prolonged ICU stay (> 2days) (Atoui et al. 2008). Other authors also noted that one of the most important factors associated with early disharge from ICU was preoperative ejection fraction (Xu et al. 2006, Ranucci et al. 2007).

Patients with depressed preoperative left ventricular function also have increased long-term mortality. A Canadian study consisting of 7,841 patients having isolated CABG showed that compared to patients with normal EF, patients having low (<30%) or moderately low (30%–50%) preoperative EF have both higher operative mortality (4.6%–3.4%–1.9%) and poorer long term prognosis at 5 years (77.7%–85.5%–91.2%) than patients with normal EF (Appoo et al. 2004). In a review considering aortic valve replacement and long term (> 5 years) prognosis, age at surgery, NYHA functional class at time of surgery, left ventricular ejection fraction, atrial fibrillation, and type of valvular lesion were independent prognostic factors of adverse outcome (Naslafkih et al. 2006). Loef in 2009 showed that preoperative EF <50% increased the mortality risk during 13-year follow-up by 1.71 (Loef et al. 2009). If preoperative left ventricular dysfunction was associated with postoperative renal dysfunction, the hazard ratio for late mortality was 3.23.

2.3 Intraoperative risk factors

2.3.1 Cardiopulmonary bypass

At the present time, there is considerable controversy surrounding the appropriate management of physiologic variables during cardiopulmonary bypass (CPB). Low-risk patients tolerate mean arterial blood pressures of 50–60 mm Hg without apparent complications, although limited data suggest that higher-risk patients may benefit from mean arterial blood pressures >70 mmHg (Charlson et al. 1995, Gold et al. 1995, Charlson et al. 2007). The optimal haematocrit on CPB has not been defined, with large data-based investigations demonstrating that both severe haemodilution (DeFoe et al. 2001, Habib et al. 2003, Karkouti et al. 2005b, Karkouti et al. 2005a, Hare 2006) and transfusion of packed red blood cells increase the risk of adverse postoperative outcomes (Karkouti et al. 2004).

Oxygen delivery is determined by the pump flow rate and the arterial oxygen content. Organ injury may be prevented during more severe haemodilutional anaemia by modifying the CPB technique or by simply increasing pump flow rates (Ranucci et al. 2005, Liebold et al. 2006). Furthermore, the optimal temperature during CPB likely varies with physiologic goals, and recent data suggest that aggressive rewarming practices may contribute to neurologic injury (Cook et al. 1996, Grocott HP. Mackensen GB. Grigore AM. Mathew J. Reves JG. Phillips-Bute B. Smith PK. Newman MF. Neurologic Outcome Research Group (NORG). Cardiothoracic Anesthesiology Research Endeavors (CARE) Investigators' of the Duke Heart Center 2002, Kaukuntla et al. 2004). The design of components of the CPB circuit may also influence tissue perfusion and outcomes. Although there are theoretical advantages to centrifugal blood pumps over roller pumps, it has been difficult to demonstrate that the use of centrifugal pumps improves clinical outcomes (Steinbrueckner et al. 1995, Baufreton et al. 1999).

CPB is associated with an acute phase reaction of protease cascades, leukocyte, and platelet activation inducing a systemic inflammatory reaction (SIRS) and resulting in tissue injury (Edmunds 1998). This is largely manifested as subclinical organ dysfunction that produces a clinical effect in those patients who generate an excessive inflammatory response or those with limited functional reserve (Khabar et al. 1997, Whitten et al. 1998) increasing morbidity and mortality after cardiac surgery (Kang et al. 2004, Salis et al. 2008). Heparin coating of the CPB circuit may attenuate inflammatory and coagulation pathways, but has not been clearly demonstrated to reduce major morbidity and mortality. Similarly, no distinct clinical benefits have been observed when open venous reservoirs have been compared to closed systems. In conclusion, there are currently limited data upon which to confidently make strong recommendations regarding how to conduct optimal CPB. (Shann et al. 2006, Murphy et al. 2009).

Hence, it is still clear that cardiopulmonary bypass techniques are not perfect. Indeed, it is fair to say that the period of bypass still contributes to significant morbidity in most patients (Khabar et al. 1997, Hogue et al. 1999, Murphy and Angelini 2004). In particular, cerebral injury is a significant problem for patients and their caregivers and for funding of health-care systems. Incidence rates for stroke are around 2% to 3% (Taylor 1998), with increased risk in elderly patients and other high-risk groups (Sotaniemi 1995).

2.3.2 *Off-pump vs. on-pump vs. mini-extracorporeal circulation*

The introduction of extracorporeal circulation in the late 1950s revolutionised the practice of modern cardiac surgery. While the use of CPB still remains essential in most cardiac operations, it sill has several disadvantages. First its use is associated with a systemic inflammatory response syndrome (SIRS) due to activation of a myriad of cellular and humoral inflammatory mediators as blood circulates through the extracorporeal circuit and blood cells make contact with the synthetic components (Hall et al. 1997). Second, cardiopulmonary bypass has been regarded as an important aetiologic factor in the generation of both particulate and gaseous microemboli which can further contribute to the development of end organ damage (Roach et al. 1996, Murkin and Stump 2000). In an attempt to ameliorate the potential deleterious effects of cardiopulmonary bypass, techniques have been created to either totally avoid bypass or build up an at least theoretically less harmful miniperfusion facility (Fromes et al. 2002, Wiesenack et al. 2004, Mulholland et al. 2007).

Kolessov was the first to report his experience with coronary artery surgery on the beating heart in 1967 (Kolessov 1967). The technique, however, was soon abandoned with the increasing availability of cardiopulmonary bypass. Later on, off-pump surgery has experienced a revival, beginning in the early 1990s with the work of Benetti and colleagues (Benetti et al. 1991) and Buffolo and colleagues (Buffolo et al. 1996). Hypothetically, off-pump surgery would be expected to result in a reduction in systemic inflammation, emboli production (at least if the aorta is not touched) and subsequent end organ dysfunction as well as avoidance of myocardial ischaemia.

So far, several meta-analyses have been conducted comparing the outcomes of revascularization with and without cardiopulmonary bypass, including both observational data and randomized controlled trials (Cheng et al. 2005, Lim et al. 2006, Marasco et al. 2008, Moller et al. 2008, Sistino 2008, Takagi et al. 2007, Feng et al. 2009). Off-pump surgery tends to be associated with a reduction in the rate of atrial fibrillation, transfusion and inotrope requirements, respiratory infections, ventilation time, intensive care unit stay and hospital stay. No significant differences were found for 30-day mortality, myocardial infarction, stroke, renal dysfunction, intra-aortic balloon pump use, wound infection, re-exploration, or re-intervention, but these studies may be biased by surgical technique and revascularization policy. It seems to be safe to conduct OPCAB procedure also on patients having poor left ventricular function. In a retrospective study of 177 patients with EF <30% OPCAB patients tolerated the procedure well and according to this study, cardiopulmonary bypass was the only predictor for all postoperative complications (Arom et al. 2000). The randomized controlled trials to date have been conducted in relatively low-risk patients who are at least risk of the deleterious effects of cardiopulmonary bypass. Møller et al. conducted a prospective study between off and on-pump in patients having >5 EuroSCORE points. Both off and on-pump coronary artery bypass grafting performed on high-risk patients with equal low short-term complications (Moller et al. 2010).

The early literature on off-pump CABG also suggested that off-pump surgery would reduce or eliminate the neuropsychological risks of putting a patient on a heart-lung bypass machine. However, the results of the 2203-patient, 18-centre Randomized On/Off Bypass (ROOBY) trial, showed no difference between the on-pump and off-pump approaches in neuropsychological outcomes (Shroyer AL. Grover FL. Hattler B. Collins JF. McDonald GO. Kozora E. Lucke JC. Baltz JH. Novitzky D. Veterans Affairs Randomized On/Off Bypass (ROOBY) Study Group 2009). The proportion of patients with fewer grafts completed than originally planned was higher with off-pump CABG than with on-pump CABG (17.8% vs. 11.1%, P<0.001). The study also showed a consistent trend toward better overall outcomes after one-year postsurgery with the on-pump approach (death within one year on-pump vs. off-pump 2.9%/4.1% and composite end points at one year 7.4%/9.9%, p0.04 respectively). Follow-up angiography in 1371 patients and a total of 4093 grafts showed that the on-pump group had a higher graft patency rate (87.8% vs 82.6%; p<0.001). Also, 36.5% of the off-pump group had at least one occluded graft compared with 28.7% of the on-pump group.

In terms of Health Related Quality of Life (HRQoL) neither traditional CABG using cardiopulmonary bypass nor the newer OPCAB technique is superior to other (Jokinen et al. 2010).The full benefits of off-pump surgery may be with those elderly, high-risk patients with significant aortic atherosclerosis, where avoiding the manipulation of the aorta yields greatest benefit.

Miniaturized CPB systems (Mini-CPB) have been introduced in clinical practice as an alternative to conventional cardiopulmonary bypass (C-CPB) and its use has been embraced with enthusiasm. Mini-CPB systems aim to minimize the blood-artificial surface contact as well as to reduce the priming volume and, thus, to maintain haematocrit over critical levels. A recent meta-analysis of randomized studies, despite the latter being of small size and including low-risk patients, suggested that Mini-CPB may be associated with a lower risk of postoperative stroke and blood losses and also with a somewhat decreased mortality (Biancari and Rimpilainen 2009). A recent study by Koivisto et al. showed that the use of Mini-CPB in high-risk patients undergoing isolated CABG can be associated with favourable outcome compared to C-CPB. Mini-CPB seems to be associated with a lower risk of in-hospital mortality, re-sternotomy for bleeding, use of intra-aortic balloon pump, combined adverse end-point and, most notably, stroke. The trend toward reduced risk of severe complications after using Mini-CPB is of particular interest. A consecutive series of 236 patients with additive EuroSCORE ≥6 were operated on employing either a conventional bypass circuit (C-CPB) or a minimized bypass circuit (Mini-CPB). In-hospital mortality in the C-CPB group was only slightly higher than in the Mini-CPB group (4.8% vs.3.4%, p=0.75). Stroke rate was significantly higher among C-CPB patients (5.4% vs. 0% in Mini-CPB, p=0.026). Combined adverse end-point was experienced more frequently by C-CPB patients (20.4% vs. 13.5%, p=0.18) as well, but the difference failed to reach statistical significance (Koivisto et al. 2010). A meta-analysis comprising 13 studies and comparing miniaturised (Mini-CPB) versus conventional cardiopulmonary bypass (C-CPB) suggests that the use of Mini-CPB may be associated with lower risk of postoperative stroke and blood losses and with somewhat decreased mortality. However, due to the wide heterogeneity of methods and the small number of studies and patients evaluated so far, larger and homogeneous studies should be performed to obtain more conclusive results on the safety and efficacy of Mini-CPB (Biancari and Rimpilainen 2009).

2.3.3 Myocardial protection

Cardioplegia is an important strategy to facilitate cardiac surgery in order to limit myocardial injury. Initially cardioplegia was introduced as an agent to allow for hypothermic hyperkalemic arrest (Tyers et al. 1977, Roe et al. 1977). Various additives were explored to try to optimize the myocardium during this time of ischaemia (Bretschneider et al. 1975). Blood was then found to be the most logical vehicle for delivery of potassium cardioplegia (Follette et al. 1978, Buckberg 1979). The optimal cardioplegic temperature, timing, and routes of delivery were further explored (Braimbridge et al. 1977, Poirier et al. 1975, Fremes et al. 2000, Buckberg 1987). Although cardioplegia is generally accepted as a mandatory tool for myocardial protection during on-pump cardiac surgery, there is still controversy regarding various aspects including its composition, temperature, and mode of delivery. Blood as opposed to crystalloid cardioplegia (CCP) could potentially improve postoperative cardiac outcomes, because it more closely approximates normal physiology due in part to its oxygen carrying capacity and less associated haemodilution (Menasche et al. 1992, Menasche and Menasche 1994, Menasche 1996). On the other hand, blood cardioplegia (BCP) may impair visualization during the operation.

The largest prospective randomised controlled trial comparing blood vs. crystalloid cardioplegia was done by Øvrum et al. in 2004. Two surgeons performed 1,440 CABG procedures randomised to either cold CCP or cold BCP. The clinical course, systemic temperature and delivery methods were unified for all patients and emergencies, redos and low EF patients were included. No differences were seen for perioperative myocardial infarction or mortality. However, the mean ischaemic time in this study was 33.5 (SD 10.0) and 34.1 (SD 9.1) min, and the duration of perfusion was 52.2 (SD 11.6) and 53.5 (SD 11.6) min for CCP and BCP patients respectively, which may limit its general applicability to more complex cardiac surgery (Ovrum et al. 2004). The other large trial was conducted by Martin et al. from 1990–1992. One thousand-and-one patients undergoing elective CABG were randomised to either (1) systemic hypothermia at 28° and intermittent 25 mmol/l potassium cold crystalloid cardioplegia or (2) antegrade high potassium (20 mmol/l) warm blood cardioplegia followed by continuous retrograde low potassium (19 mmol/l) warm blood cardioplegia. There was an unexpectedly high rate of perioperative strokes, delayed strokes and total neurologic events in the warm blood cardioplegia arm, which caused the study to be discontinued prematurely. At this stage there were no differences in mortality, IABP use, inotrope use, or hospital stay (Martin et al. 1994). Both the equivalent myocardial outcomes and adverse neurological outcomes may be explained in terms of temperature rather than cardioplegic solution.

Fremes' Toronto group in 2006 performed a meta-analysis of 34 randomised controlled trials comparing crystalloid to blood cardioplegia. Most of the studies were of small size, and there were only two with more than 1,000 patients in total and another three with more than 100 patients in the blood cardioplegia arm. In total there were 5,000 patients included in these studies (but of these, half were from two studies). They reported that the incidence of low output syndrome was significantly lower with BCP with an odds ratio of 0.54 (95% CI 0.34–0.84), and the CK-MB release was higher with CCP at 24 hours by a weighted mean difference of 5.7 U/l at 24 h (95% CI 1.6–10.2). There was no difference in the aggregated myocardial infarction or mortality rates. However, firm conclusions are difficult to draw from these findings as the authors were unable to obtain any data on low output syndrome or CK-MB from the two studies with more than 1,000 patients and thus the low output finding was based on only 10 of the 34 trials (879 patients), and the CK-MB findings came from only seven trials (Guru et al. 2006).

Jacob et al. expanded the series of randomised trials gathered by Fremes' group with 15 additional studies. Of these, eight reported statistically significant clinical outcomes in favour of BCP and five reported statistically significant differences in enzyme release in favour of BCP. No studies reported findings in favour of CCP (Jacob et al. 2008).

Thus, the literature is far from conclusive. This is reflected in a survey of practice in the UK of 2004 which found that of the surgeons performing on-pump CABG, 56% used cold blood cardioplegia, 14% used warm blood cardioplegia, 14% used crystalloid cardioplegia, 21% used retrograde infusion and 16% did not use any cardioplegia, preferring cross-clamp fibrillation (Karthik et al. 2004).

Scarci et al. conducted a meta-analysis of intermittent cross-clamping compared to either blood or crystalloid cardioplegia. They stated that intermittent cross-clamp fibrillation was a versatile and cost-effective method of myocardial protection in first-time CABG, with the immediate postoperative outcome comparable to cardioplegic arrest. The duration of ischaemia associated with intermittent cross-clamp fibrillation is invariably shorter than that associated with cardioplegic arrest, and this may be one explanation for the comparable outcomes. There may also be an element of preconditioning protection during intermittent cross-clamp fibrillation, as has been shown experimentally (Fujii,Masahiro 2005, Scarci et al. 2009).

2.3.4 Duration of aortic cross-clamp and perfusion

A long aortic cross-clamp time and hence at least suboptimal oxygenation of the heart are known to be major risk factors. Kirklin in a summary of a consensus on death and ischaemic events after coronary artery bypass grafting noted that aortic cross-clamp time, among several other factors, was an incremental risk factor (Kirklin et al. 1989). A longer aortic cross clamp time was a risk factor for myocardial infarction during coronary artery bypass graft surgery in a study by Oysel et al. (Oysel et al. 1989). In a recent study by Onorati et al. an additive EuroSCORE greater than 6, ongoing unstable angina, aortic cross-clamp time longer than 90 minutes, cardiopulmonary bypass time longer than 180 minutes, incomplete revascularization, and intraoperative intraaortic balloon pump were independent predictors of myocardial damage at multivariate analysis (Onorati et al. 2005).

Despite many years of clinical and experimental research, the contribution of cardiopulmonary bypass (CPB) and cardioplegic arrest to morbidity and mortality following cardiac surgery remains unclear. This is due, in part, to a lack of a suitable control group against which bypass and cardioplegic arrest can be compared. The recent success of beating heart coronary artery bypass grafting has, however, provided an opportunity to compare the same operation, in similar patient groups, with, or without CPB and cardioplegic arrest. CPB is associated with an acute phase reaction of protease cascades, leukocyte, and platelet activation that results in tissue injury. This is largely manifested as subclinical organ dysfunction that produces a clinical effect in those patients who generate an excessive inflammatory response or in those with limited functional reserve (Murphy and Angelini 2004). This systemic inflammatory response syndrome (SIRS) is a complex array of clinical conditions including hypotension, coagulopathy, and increased capillary permeability. At worst the situation can lead to multiple organ dysfunction syndrome (Khabar et al. 1997).

The detrimental effects of CPB have also been attributed to reinfusion of cardiotomy suction blood exposed to pericardial and mediastinal surfaces, the presence of microemboli (gaseous or particulate) and foreign material in the CPB circuit (Salis et al. 2008). The contribution of myocardial ischaemia/reperfusion, secondary to aortic cross-clamping, and cardioplegic arrest, to the systemic inflammatory response and wider organ dysfunction is unknown, and requires further evaluation in clinical trials (Murphy and Angelini 2004).

It is reasonable to assume that the longer the CPB duration, the worse its detrimental effects will be. Andersson et al. identified CPB longer than 150 minutes as one of the independent predictors of major GI complications (Andersson et al. 2005). Perugini et al. similarly found that in patients who underwent CABG surgery only, CPB time was significantly longer in patients with GI complications (166 vs. 138 min, $p=0.004$) (Perugini et al. 1997). Some other studies were unable to confirm this finding, possibly because of the infrequent nature of GI complications (0.7%) (Salis et al. 2008). Salis et al. showed that CPB time is an independent risk factor for postoperative death (OR 1.57), pulmonary (OR 1.31), renal (OR 1.31), and neurologic complications (OR 1.28), multiorgan failure (OR 1.21), reoperation for bleeding (OR 1.1) and multiple blood transfusions (OR 1.58) (Salis et al. 2008). In a material from St. Louis, Hogue et al. found the incidence of strokes to be 1.6% among 2,972 patients undergoing cardiac surgery. They divided strokes into early, occurring immediately after surgery, and delayed (65% of all) after an initial uneventful neurological recovery. By multivariate analysis, prior neurological event, aortic atherosclerosis, and duration of CPB were independently associated with early stroke, whereas CPB time was not connected to delayed neurological events (Hogue et al. 1999). Bucerius, in a multivariate analysis of over 16,000 cardiac surgery patients found CPB time more than 2 hours to be independent predictor for stroke.

Ranucci et al. in 2007 observed that factors associated with late discharge from ICU were age, preoperative serum creatinine value, unstable angina, congestive heart failure, redo operation, combined operation, and cardiopulmonary bypass duration (Ranucci et al. 2007).

2.3.5 Perioperative versus ICU risk assessment

Morbidity and mortality are influenced by surgical, anaesthetic and perfusion techniques that include aortic crossclamp time, length of time on cardiopulmonary bypass, completeness of revascularization, adequacy of myocardial protection, and haemodynamic management. Intraoperative events can both neutralize or amplify the risk calculated preoperatively.

The majority of scoring models rely solely on preoperative anamnesis and investigations. A methodology in order to more accurately predict hospital mortality risk for critically ill hospitalized adults was developed 1978 by William A. Knaus. It is known as APACHE (Acute Physiology, Age, Chronic Health Evaluation) and a third version is in current use. There are four components: age, major disease category (reason for ICU admission), acute (current) physiology, and prior site of healthcare (e.g., hospital floor, emergency room, etc.). The physiologic variables require scoring of the following vital signs and laboratory abnormalities: pulse rate, mean blood pressure, temperature, respiratory rate, PaO2/P(A-a)O2, haematocrit, white blood cell count, creatinine, urine output, blood urea nitrogen, serum sodium, albumin, bilirubin, glucose, acid-base status and neurologic status. Other models for evaluating physiologic reserve and risk for intensive care unit patients are “the Mortality Probability Model” (MPM) developed by Lemeshow (Lemeshow et al.) and SAPS, presented by Le Gall (Le Gall et al. 1993), both based on the same principles as APACHE.

2.4 Operative risk indices and their clinical use

The prediction of the risk of adverse peri- and postoperative outcome is of paramount importance in cardiac surgery as it may guide the decision-making process towards cardiac surgery or towards other currently available treatment methods. Risk prediction helps in planning resource utilisation, it is useful in comparison between different institutions and, especially, is an estimate of the individual patient's risk. Compared to conservative treatment methods, surgical interventions carry a higher degree of risk and the proposed benefit of an intervention must be weighed against a valid risk estimate. Growing concern among the medical profession induces the drastically changing landscape where cardiac surgery is nowadays performed and where (old) models for risk adjustment are proving imprecise. This evolution has been driven by a changing patient population but also by the expansion of interventional cardiology, catheter-based interventions, and minimally invasive cardiac procedures.

Variations in results between institutions can also be significant making comparison between institutions problematic (Nashef 2009).

In recent decades, several risk-scoring methods have been derived and validated with varying success. (Nilsson et al. 2006). With all risks in mind there is a great desire for models to predict mortality and morbidity. Predicting the risk of mortality for an individual patient might seem like the most obvious reason to use a predictive model. However, this approach has its drawbacks. Not the least of which is that the models available are derived from a study of large populations including a great number of different variables not necessarily fitting the particular individual. A variety of factors are in play causing these models to be inaccurate. These are the skill and experience of the surgical team, institution-specific issues, comorbidities not included in the calculation of risk, magnitude of the cardiac procedure and the misinforming possibility of gathered risk profile when numerous variables are included in an attempt to control or adjust the data (Granton and Cheng 2008, Ranucci et al. 2009).

2.4.1 Comparison of some commonly used algorithms

Parsonnet Score

The Parsonnet score was developed in the United States in the 1980s (Parsonnet et al. 1989). The database used was 3,500 consecutive operations, and an additive model was constructed to predict 30-day mortality (Parsonnet,V. 1989). The Parsonnet score divides patients into 5 risk groups based on the score accumulated from 16 different preoperative variables. However, there was a major criticism of the model. Two of the variables (catastrophic states and other rare circumstances) were fairly arbitrary and could significantly influence the score (Gabrielle et al. 1997). To help address this issue a modified Parsonnet's score was developed. It is far more detailed than the original scoring system and includes a wide variety of what could be classified as catastrophic states and rare circumstances. However, the complexity of the modified score is far greater than the original, making it somewhat more difficult to use.

Since its publication in 1989, the Parsonnet score has received widespread acceptance and has been heavily studied and used. A criticism of the Parsonnet score is that it often overpredicts mortality (Geissler et al. 2000). Possibly due to the age of the Parsonnet score the predictive accuracy has been diminished as a result of advances in surgical and medical techniques. One of the confusing aspects of comparing scoring systems is that it may be difficult to understand if the modified or initial Parsonnet score is being used while reading a report.

Cleveland Clinic Model

In 1992, the Cleveland Clinic model for risk stratification in CABG surgery was published (Higgins et al. 1992c). It was developed from a retrospective analysis of 5,051 patients undergoing CABG in the mid to late 1980s at the Cleveland Clinic. The model was also validated at the same centre. This model was developed not only to look at mortality but also morbidity in CABG patients. These aspects of morbidity included myocardial infarction, prolonged mechanical ventilation, renal failure, neurologic injury, serious infection, and the need for an intraaortic balloon pump. A variety of risk factors were identified and an additive score was developed based on these risk factors. When compared to other risk stratification systems, the Cleveland Clinic risk score performs within an acceptable range (Nilsson et al. 2006). However, as with many scoring systems, the Cleveland Clinic score is not perfect. It has been shown to underpredict mortality (Pinna-Pintor et al. 2002). Likely due to its original design, the Cleveland Clinic score does show a better performance in the prediction of morbidity when compared with the EuroSCORE, Parsonnet, and a variety of other scoring systems (Geissler et al. 2000).

Society of Thoracic Surgeons Score (STS Score)

The Society of Thoracic Surgeons (STS) initially developed the STS National Adult Cardiac Surgery Database (STS NCD) in the late 1980s. After many years of development and improvement, it has become one of the largest clinical databases in the world. The STS began building risk models in 1994 (Edwards et al. 1994b). A series of additional models have been developed since then to keep the predictive models timely, accurate, and thus more reliable. Risk models now also include risk of death for isolated valve or valve concomitant with CABG operations as well as several morbidity risk models. The STS NCD has completely redeveloped its risk models approximately every 3 years. The latest models, the "2008 Models," were developed using data collected from 2002 to 2006 (O'Brien et al. 2009, Shahian and Edwards 2009, Shahian et al. 2009a, Shahian et al. 2009b) and comprise 27 models, including nine endpoints for each of three cardiac procedure groups:

Procedures:
1. Isolated CABG
2. Isolated valve procedure (aortic valve replacement; mitral valve replacement or repair)
3. Isolated valve procedure plus CABG

Endpoints:
1. Operative mortality
2. Reoperation for any reason
3. Permanent stroke

4 Renal failure
5 Deep sternal wound infection
6 Prolonged ventilation time (>24 hours)
7 Operative death or major morbidity (of the five types above)
8 Short postoperative length of stay (<6 days and discharged alive)
9 Long postoperative length of stay (>14 days)

From 1999 until now, the STS has released four versions of the STS NCD, and the built-in models were changed accordingly. Thus, patients with exactly the same preoperative risk factors could receive different predicted risk values if they underwent surgery in different time periods. Moreover, the individual patient risk scores require calibration, using the STS-provided calibration factors (CF) before they can be used to compute observed (O)/expected (E) ratios or compare provider performance over time. Calibration factors are updated after every new data harvest, which has been done every 3 months in recent years. The reason for these frequent changes is that the STS uses all data available up to the point of harvest to recalculate the CFs for a given year. Thus, to calibrate the predicted STS risk, one must always find the latest report and use the most recent CFs.

Unfortunately, one of the most complete studies done to date, comparing 19 scoring systems, does not include the STS risk stratification algorithm, because it was not considered an open source (Nilsson et al. 2006). In a single institution Swedish study, Nilsson et al. found that the EuroSCORE and the STS algorithm showed similar accuracy, but the EuroSCORE demonstrated greater discriminative capability for CABG (Nilsson et al. 2004b). In general, the predictive performance of the STS algorithm is comparable to the other scoring systems (Farrokhyar et al. 2007, Ad et al. 2007).

The web address for STS score calculator is: http://209.220.160.181/STSWebRiskCalc261/

EuroSCORE

The EuroSCORE was initially published in 1999 (Nashef et al. 1999). It was developed from a large European database including 19,030 patients from 128 hospitals. Information on 97 risk factors was collected pre-operatively in all the patients (Roques et al. 1999). The risk factors were then compared to patient outcomes (survival or death) leaving 17 risk factors related to the patient, cardiac status and operation and known to affect outcome (Table 5). This original additive model allocates an appropriate weight for each risk factor resulting in a score intended to predict mortality. However, it was felt that this model had some drawbacks. First, an overprediction of mortality may occur in low-risk cases (Roques et al. 1999, Gogbashian et al. 2004a, Bhatti et al. 2006). Second, the additive model has conversely also been shown to be a poor predictor of mortality in high-risk patients (Roques et al. 2003b, Gogbashian et al. 2004a). There was therefore an incentive to develop a more accurate scoring system to cover a wider population of cardiac surgery patients. By means of logistic regression calculations, those risk factors that were most robust in predicting mortality became part of the logistic EuroSCORE calculation. Thus two different scoring systems exist for the EuroSCORE. One is the additive model, which can be calculated by simple aritmetic. The other is the logistic model, which is more extensive and requires a computer to derive a score. In further subdivision of the high-risk group, the logistic EuroSCORE seems to predict mortality with acceptable accuracy (Michel et al. 2003b).

This scoring system is used extensively in Europe and is also popular in Canada (Roques et al. 2003a, Kolh 2006). Several studies have been performed to evaluate the accuracy, calibration and (international) clinical performance of EuroSCORE. In a review of six articles, Gogbashian et al. confirmed that the additive EuroSCORE overestimates mortality at lower EuroSCOREs (EuroSCORE <6) and underestimates mortality at higher EuroSCOREs (EuroSCORE >13) (Gogbashian et al. 2004a). In an extensive comparison of 19 pre-operative risk stratification models in adult open heart surgery, Nilsson et al. studied their validity to predict both 30-day and 1-year mortalities after cardiac surgical procedures (Nilsson et al. 2006). Their study included 6,222 cardiac operations performed between 1996 and 2001 at a single Swedish institution, with prospective data collection. They used receiver-operating characteristic (ROC) curves to describe the performance and accuracy of the risk-scoring algorithms. An area under the curve >70% is usually considered to be associated with a good predictive value. For overall

Table 5. Patient- and cardiac-related factors contributing to the Additive EuroSCORE

Patient-related factors		Score
Age	(per 5 years or part thereof over 60 years)	1
Sex	female	1
Chronic pulmonary disease	longterm use of bronchodilators or steroids for lung disease	1
Extracardiac arteriopathy	any one or more of the following: claudication, carotid occlusion or >50% stenosis, previous or planned intervention on the abdominal aorta,limb arteries or carotids	2
Neurological dysfunction disease	severely affecting ambulation or day-to-day functioning	2
Previous cardiac surgery	requiring opening of the pericardium	3
Serum creatinine	>200m micromol/L preoperatively	2
Active endocarditis	patient still under antibiotic treatment for endocarditis at the time of surgery	3
Critical preoperative state	any one or more of the following: ventricular tachycardia or fibrillation or aborted sudden death, preoperative cardiac massage, preoperative ventilation before arrival in the anaesthetic room, preoperative inotropic support, intraaortic balloon counterpulsation or preoperative acute renal failure (anuria or oliguria<10 ml/hour)	3
Cardiac-related factors		**Score**
Unstable angina	rest angina requiring iv nitrates until arrival in the anaesthetic room	2
LV dysfunction	moderate or LVEF30-50% poor or LVEF <30	1 3
Recent myocardial infarct	(<90 days)	2
Pulmonary hypertension	Systolic PA pressure>60 mmHg	2
Operation-related factors		**Score**
Emergency	carried out on referral before the beginning of the next working day	2
Other than isolated CABG	major cardiac procedure other than or in addition to CABG	2
Surgery on thoracic aorta	for disorder of ascending, arch or descending aorta	3
Postinfarct septal rupture		4

open-heart surgery, Nilsson et al. report that discriminatory power for 30-day and 1-year mortalities was highest for logistic (0.84 and 0.77) and additive (0.84 and 0.77) EuroSCORE algorithms. The next highest was the Cleveland Clinic score (0.82 and 0.76). Furthermore, in coronary artery bypass grafting (CABG)-only surgery (4,351 procedures), Euro-SCORE had the highest discriminatory power both for 30-day and 1-year mortalities. The finding that EuroSCORE, probably the most commonly used scoring algorithm in Europe, can accurately predict operative mortality after open-heart surgery and after CABG-only procedures confirms the results of earlier studies (Nashef,S.A. 2000; 386 Asimakopoulos,G. 2003). Furthermore, despite substantial geographic differences between Europe and North America, EuroSCORE performs very well in the Society of Thoracic Surgeons database (Asimakopoulos et al. 2003, Nashef et al. 2000). Therefore, it can be considered an adequate risk stratification system on both sides of the Atlantic (Nashef et al. 2000).

Long-term mortality, probably the most useful outcome, is rarely assessed, essentially because of the difficulty in following up patients over a long period of time. It certainly should be a priority for future research in risk modelling. In this regard, the findings by Nilsson et al. that some risk stratification models, such as EuroSCORE, can predict 1-year mortality is potentially important, but requires further validation. Also, in another long-term (mean 10.7 years) follow-up study Biancari et al. stated that both additive and logistic EuroSCORE are good predictors of both short-term and long-term survival (Biancari et al. 2006).

EuroSCORE has also been shown to predict long-term health-related quality of life after CABG. Loponen et al. in 2008 in a prospective material of 302 patients conducted a three-year follow-up and found that both additive and logistic EuroSCORE correlated significantly with the 15D quality of life-score at 6, 18 and 36 months (Loponen et al. 2008). The best cut-off value of the additive EuroSCORE for prediction of a clinically important improvement of the 15D score during 3-year follow-up was 3, as 46.7% of patients with EuroSCORE 0-3 and 30.1% of patients with a score >3 ($P=0.006$) improved clinically.

The web address for EuroSCORE calculator is: http://www.euroscore.org/calc.html

3 AIMS OF THE STUDY

The aims of the present study were:

To estimate the accuracy of preoperative pulmonary function testing (I–II).

To investigate short and long term results of cardiac surgery in older patients (III).

To investigate the safety limits of current cardiac surgery practice in terms of aortic cross-clamp time and perfusion time (IV).

To derive and validate a more precise risk scoring algorithm from the current EuroSCORE (V–VI).

4 LIST OF ORIGINAL PUBLICATIONS

This dissertation is based on the following original articles, which are referred to in the text by Roman numerals:

I Nissinen J, Biancari F, Wistbacka JO, Niemi R, Loponen P, Tarkiainen P, Tarkka M. Pulmonary function and immediate outcome of patients undergoing aortic valve replacement. J Heart Valve Dis 2009;18:374–379.

II Nissinen J, Biancari F, Wistbacka JO, Loponen P, Kairi P, Korpilahti K, Tarkka M. Pulmonary function and immediate and late outcome after coronary artery bypass surgery. J Cardiovasc Surg (accepted, in press).

III Nissinen J, Wistbacka JO, Loponen P, Korpilahti K, Teittinen K, Virkkilä M, Tarkka M, Biancari F. Coronary artery bypass surgery in octogenarians: long-term outcome can be better than expected. Ann Thorac Surg 2010;89:1119–1124.

IV Nissinen J, Biancari F, Wistbacka JO, Peltola T, Loponen P, Tarkiainen P, Virkkilä M, Tarkka M. Safe time limits of aortic cross-clamping and cardiopulmonary bypass in adult cardiac surgery. Perfusion 2009;24:297–305.

V Nissinen J, Biancari F, Wistbacka JO, Loponen P, Teittinen K, Tarkiainen P, Koivisto SP, Tarkka M. Is it possible to improve the accuracy of EuroSCORE? Eur J Cardiothorac Surg 2009;36:799–804.

VI Biancari F, Laurikka J, Wistbacka JO, Nissinen J, Tarkka M. External validation of modified EuroSCORE. World Journal of Surgery (accepted, in press).

5 MATERIALS AND METHODS

Studies I–V deal with a consecutive series of 4,563 patients who underwent adult cardiac surgery at Vaasa Central Hospital, Vaasa, Finland, from January 1994 to June 2008. Study VI deals with a series of 4,014 adult patients who underwent cardiac surgery at the Heart Center of Tampere University Hospital, Tampere, Finland, from January 2004 to December 2008.

Clinical and operative data

Variables are categorized according to the EuroSCORE criteria (Roques 1999). Operative risk was estimated according to EuroSCORE (Roques 1999) and Cleveland risk score (Higgins 1992). The data of these patients were collected prospectively into an institutional cardiac surgery database. Studies I–V were approved by the Ethics Committee of Vaasa Central Hospital and a waiver of the requirement of written informed consent was obtained for Study III.

Studies I and II

The characteristics and operative data of the patients included in Studies I–II are summarized in Table 1. Study I included a series of 453 patients who underwent spirometry immediately before AVR operation with or without CABG at Vaasa Central Hospital, Vaasa, Finland, from January 1996 to June 2008. Patients who underwent any other concomitant heart valve operation as well as surgery on the ascending aorta were excluded from this analysis. Study II included 1,848 patients who underwent isolated CABG during the same period. Pulmonary disease was classified as use of bronchodilators or steroids for COPD/asthma. Spirometry was

Table 6. Preoperative and operative data on patients included in Studies I–II.

Variables:	Study I No. (%)	Study II No. (%)
Age (years)	69±11	67.8±9.4
Females	186 (41)	453 (24.5)
Percentages of predicted FEV1	88±17	83.9±17.6
Percentages of predicted FVC	82±18	89.5±16.6
History of smoking	115 (23)	734 (39.7)
Pulmonary disease	61 (14)	225 (12.2)
Diabetes	70 (16)	409 (22.1)
Serum creatinine	90±41	93.3±45.3
Neurological dysfunction	3 (1)	25 (1.4)
Myocardial infarction<3 months	17 (4)	275 (14.9)
Extracardiac arteriopathy	23 (5)	182 (9.8)
Previous cardiac surgery	18 (4)	78 (4.2)
Unstable angina pectoris	6 (1)	72 (3.9)
Critical preoperative status	6 (1)	5 (0.3)
Active endocarditis	7 (2)	-
Systolic pulmonary a. pressure >60 mmHg	14 (3)	10 (0.5)
Emergency operation	3 (1)	16 (0.9)
Indication for surgery:		
Aortic valve stenosis	281 (62)	-
Aortic valve regurgitation	64 (14)	-
Combined aortic valve disease	98 (22)	-
Others	10 (2)	-
Additive EuroSCORE	6±3	3.8±2.5
Logistic EuroSCORE (%)	7±8	3.9±4.1

a: Definition criteria for preoperative variables are according to EuroSCORE;
b: classified as use of bronchodilators or steroids for COPD/asthma;
LVEF: left ventricular ejection fraction; Continuous variable are reported as the mean ± standard deviation;

Table 7. Clinical and operative data of patients aged ≥80 years and <80 years and who underwent isolated coronary artery bypass surgery (Study III).

	Overall series			Propensity score matched pairs		
	Octo-genarians	Younger patients	p-value	Octo-genarians	Younger patients	p-value
	274 patients (%)	3200 patients (%)		273 patients (%)	273 patients (%)	
Age (years)	82.5±1.9	66.6±8.8	<0.0001	82.5±1.9	70.5±6.8	<0.0001
Females	110 (40.1)	761 (23.8)	<0.0001	109 (39.9)	109 (39.9)	1.00
Pulmonary disease	24 (8.8)	356 (11.1)	0.23	24 (8.8)	37 (13.6)	0.08
Diabetes	63 (23.0)	618 (19.3)	0.14	63 (23.1)	69 (25.3)	0.55
Renal failure	3 (1.1)	28 (0.9)	0.73	3 (1.1)	4 (1.5)	0.73
Cerebrovascular disease	42 (15.3)	373 (11.7)	0.07	41 (15.0)	43 (15.8)	0.81
Neurological dysfunction	5 (1.8)	34 (1.1)	0.25	5 (1.8)	3 (1.1)	0.73
Myocardial infarction<3 months	106 (38.7)	628 (19.6)	<0.0001	105 (38.5)	105 (38.5)	1.00
Extracardiac arteriopathy	30 (10.9)	270 (8.4)	0.16	30 (11.0)	26 (9.5)	0.57
Previous cardiac surgery	0 (0)	126 (3.9)	<0.0001	0 (0)	17 (6.2)	<0.0001
LVEF≤50%	89 (32.5)	10 (34.2)	0.56	89 (32.6)	98 (35.9)	0.42
Unstable angina pectoris	53 (19.3)	417 (13.0)	0.003	53 (19.4)	58 (21.2)	0.60
Critical preoperative status	6 (2.2)	33 (1.0)	0.08	6 (2.2)	11 (4.0)	0.22
Systolic pulmonary artery pressure>60 mmHg	2 (0.7)	18 (0.6)	0.67	2 (0.7)	3 (1.1)	0.69
Emergency operation	21 (7.7)	180 (5.6)	0.17	21 (7.7)	29 (10.6)	0.24
Additive EuroSCORE	7.6±2.4	3.9±2.7	<0.0001	7.6±2.4	5.6±3.0	<0.0001
Logistic EuroSCORE (%)	10.6±9.3	4.3±5.6	<0.0001	10.6±9.6	7.0±8.2	<0.0001
Cleveland score	3.8±2.2	2.4±2.4	<0.0001	3.8±2.2	3.5±2.8	0.002
At least one mammary artery graft	220 (80.3)	2986 (93.3)	<0.0001	219 (80.2)	219 (80.2)	1.00
Bilateral mammary artery graft	3 (1.1)	515 (16.1)	<0.0001	2 (0.2)	2 (0.2)	1.00
No. of distal anastomoses	4.1±1.1	4.1±1.3	0.61	4.1±1.1	3.9±1.2	0.13
Beating heart surgery	54 (19.7)	288 (9.0)	<0.0001	53 (19.4)	53 (19.4)	1.00
Aortic cross-clamping time (min)	71±30	80±28	<0.0001	71±30	73±31	0.50
Cardiopulmonary bypass time (min)	101±24	103±31	0.44	101±24	105±34	0.45

*: Definition criteria for preoperative variables are according to EuroSCORE;
LVEF: left ventricular ejection fraction;
Continuous variables are reported as mean±standard deviation. Values in parentheses are percentages.

performed preoperatively in all these patients. Percentages of the predicted forced vital capacity (FVC) and percentages of the predicted forced expiratory volume in one second (FEV1) were calculated according to normal values of the Finnish population as reported by Viljanen and colleagues (Viljanen 1982). These values were estimated without bronchodilator test. Severity of pulmonary disease was graded in Study II according to the GOLD classification: Stage I FEV1≥80% of predicted; Stage II 50%≤FEV1<80% of predicted; Stage III 30%≤FEV1<50% of predicted; and Stage IV FEV1<30% (Rabe et al. 2007).

Study III

Study III included a consecutive series of 274 patients aged ≥ 80 years (only one patient was 90 years old) who underwent isolated CABG from 1994 to 2008 at Vaasa Central Hospital, Vaasa, Finland. These patients belong to a series of 3,474 patients who underwent isolated CABG during the study period. No attempt was made to replace missing values. Data on these patients are summarized in Table 7.

Study IV

Study IV included a series of 3,280 patients who underwent any adult cardiac surgery. The aim of this study was to evaluate the impact of aortic cross clamp time (XCT) and cardiopulmonary bypass time (CPBT) on immediate outcome after adult cardiac surgery performed using cardiopulmonary bypass. In order to estimate the impact of complex surgery on the immediate and late outcome, we categorized major cardiac procedures as isolated, double or a combination of three to four procedures. This may reflect a longer XCT and CPBT and, likely, more technically demanding procedures. Herein, we refer to isolated or multiple procedures according to the number of procedures on each major anatomical structure (coronary arteries, heart valves, ascending aorta/aortic arch, atrial or ventricular septum). Surgery for cardiac tumours was considered a major cardiac procedure. Preoperative data on these patients are summarized in Table 8, and data on surgery and perfusion are seen in Table 9.

Table 8. Preoperative clinical characteristics and their impact on 30-day mortality according to univariate analysis and logistic regression in a series of 3,280 patients who underwent adult cardiac surgery using cardiopulmonary bypass (Study IV).

Clinical variables	No. (%)	Univariate analysis p-value	Logistic regression O.R, 95%C.I.
Age (years)	67.4±10.4	<0.0001	<0.0001, 1.076, 1.037–1.116
Females	944 (28.8)	0.001	
Pulmonary disease	352 (10.7)	<0.0001	0.001, 2.711, 1.485–4.948
Diabetes	618 (18.8)	0.001	
Cerebrovascular disease	348 (10.6)	0.001	
Neurological dysfunction	41 (1.3)	0.08	0.021, 4.631, 1.266–16.938
Extracardiac arteriopathy	251 (7.7)	0.005	
Serum creatinine (mmol/L)	94.0±49.4	<0.0001	
Renal failure	35 (1.1)	0.002	
Estimated glomerular filtration rate ml/min/1.73 m2	74.5±19.5	<0.0001	0.003, 1.798, 1.044–3.096
Chronic kidney disease classification		<0.0001	
Classes 1–2	2573 (78.4)		
Class 3	668 (20.4)		
Classes 4–5	39 (1.2)		
Active endocarditis	19 (0.6)	0.001	
Myocardial infarction<3 months	626 (19.1)	<0.0001	
Previous cardiac surgery	120 (3.7)	<0.0001	
LVEF>50%	2180 (66.5)	<0.0001	
30–50%	967 (29.5)		0.34, 1.798, 1.044–3.096
<30%	133 (4.1)		0.071, 2.437, 0.927–6.407
Nitrates infusion at OR arrival	359 (10.9)	<0.0001	
Critical preoperative status	62 (1.9)	<0.0001	<0.0001, 8.274, 3.971–17.240
Systolic pulmonary a. pressure>60 mmHg	82 (2.5)	<0.0001	
Emergency operation	171 (5.2)	<0.0001	
Postinfarct ventricular septal rupture	9 (0.3)	<0.0001	
Additive EuroSCORE	4.8±3.1	<0.0001	
Logistic EuroSCORE (%)	5.9±8.7	<0.0001	

Continuous variables are reported as the mean±standard deviation;
LVEF: left ventricular ejection fraction;
OR: operating room.

Table 9. Operative and perfusion data and their impact on 30-day mortality according to univariate and multivariate analysis in a series of 3280 patients who underwent adult cardiac surgery using cardiopulmonary bypass (Study IV).

Operative/perfusion variables	No. (%)	Univariate analysis p-value	Logistic regression p-value, O.R, 95%C.I.
Type of operation			
Isolated CABG	2422 (73.8)		
CABG + ventriculoplasty	15 (0.5)		
CABG + AVR	245 (7.5)		
CABG + MV surgery	72 (2.2)		
CABG + double valve surgery	20 (0.6)		
CABG + triple valve surgery	3 (0.1)		
CABG + other major cardiac procedures	9 (0.3)		
CABG + other non cardiac procedures	11 (0.3)		
Isolated AVR	236 (7.2)		
Isolated MV surgery ± ASD closure	124 (3.8)		
Double valve surgery	24 (0.7)		
Triple valve surgery	7 (0.2)		
Bentall-DeBono procedure ± CABG	50 (1.5)		
Other aortic procedures	2 (0.1)		
Tricuspid valve surgery + other procedures	3 (0.1)		
Isolated ASD closure	20 (0.6)		
Isolated VSD closure	4 (0.1)		
Other major cardiac procedures	13 (0.4)		
No. major cardiac procedures*		<0.0001	0.001, 2.43, 1.41–4.19
1	2820 (86.0)		
2	404 (12.3)		
3–4	56 (1.7)		
Surgery on the thoracic aorta	56 (1.7)	<0.0001	
Procedures other than isolated CABG	854 (26.0)	<0.0001	
Aortic cross-clamping time (min)	91±36	<0.0001	<0.0001, 0.97, 0.96–0.99**
Cardiopulmonary bypass (CPB) duration (min)	117±48	<0.0001	<0.0001, 1.03, 1.02–1.04
Total potassium/magnesium administered through cardioplegia (ml); K+ 1mmol/ml, Mg2+ 0.25mmol/ml	40.2±21.2	0.067	
Lowest cardioplegia temperature (°C)	28.3±2.1	0.18	
Maintenance cardioplegia temperature (°C)	28.9±1.9	0.19	
Crystalloid component of cardioplegia (ml)	493±253	0.006	
Lowest systemic temperature during CPB (°C)	32.9±1.5	<0.0001	
Highest plasma level of K+ during CPB (mmol/l)	5.7±0.8	0.31	
Lowest haematocrit during CPB (%)	22±0.0	<0.0001	0.03, 0.92, 0.85–0.99

Continuous variables are reported as the mean±standard deviation; CABG: coronary artery bypass grafting; AVR: aortic valve replacement; MV: mitral valve; ASD: atrial septal defect; VSD: ventricular septal defect: *: We refer to isolated or multiple procedure according to the number of procedures on each major anatomical structure (coronary arteries, heart valves, ascending aorta/aortic arch, atrial or ventricular septum); **: Both cardiopulmonary bypass time and aortic cross-clamping time entered the regression model and correlation matrix showed their strong and negative correlation. For a separate analysis refer to the results section.

Study V

This study included a series of 3,613 patients undergoing any major adult cardiac surgery. These patients belong to a series of 4,563 patients undergoing cardiac surgery during the study period. The only exclusion criterion was lack of preoperative data on serum creatinine and left ventricular ejection fraction. Patients undergoing isolated minor procedures such as pericardiectomy or for arrhythmias were also excluded. No attempt was made to replace missing values.

Preoperative glomerular filtration rate was estimated according to the modified Modification of Diet in Renal Disease study equation (Levey 2000, Levey 2003)(Levey et al. 2003): eGFR (ml/min/1.73 m2) = 186 x (serum creatinine (mg/dl))-1.154 x (age)-0.203 x 0.742 (if the subject is female) x 1.212 (if the subject is black). Severity of renal failure was classified according to the chronic kidney disease (CKD) classification (Levey et al. 2003): class 1 (normal): eGFR > 90 ml/min/1.73 m2; class 2 (mild): eGFR 60–89 ml/min/1.73 m2; class 3 (moderate): eGFR 30–59 ml/min/1.73 m2; class 4 (severe); eGFR 15–29 ml/min/1.73 m2, class 5 (kidney failure): eGFR < 15 ml/min/1.73 m2. Into the regression analysis we entered three groups of patients: classes 1–2, class 3 and classes 4–5.

We classified patients' age into four classes (<60 years, 60–69.9 years, 70–79.9 years, and ≥80 years) as this classification was associated with a more evident increase in operative risk than the additive EuroSCORE age classes. Indeed, octogenarians and nonagenarians represent a relatively small number of high risk patients whose age-related risk can be represented in only one class.

In the original EuroSCORE, non-coronary surgery was considered a predictor of adverse outcome, despite the fact that patients with few or no comorbidities may undergo any other isolated major cardiac procedure without significantly higher mortality risk. In order to better estimate the impact of complex surgery on the immediate outcome, we categorized major cardiac procedure as isolated, double or a combination of three or more procedures. This may reflect a longer CPB duration and, not infrequently, more technically demanding procedures. Herein we refer to isolated or multiple procedure according to the number of procedures for each major area (coronary arteries, heart valves, ascending aorta/aortic arch, atrial

Table 10. Clinical characteristics and operative data of patients included in Study V.

	No. (%)
Age (years)	67.7±10.3
Age≥70 years	1705 (47.2)
Females	1028 (28.5)
Pulmonary disease	404 (11.2)
Diabetes	695 (19.2)
Cerebrovascular disease	396 (11.0)
Extracardiac arteriopathy	304 (8.4)
Serum creatinine (mmol/L)	94.8±49.4
Renal failure	41 (4.4)
Estimated glomerular filtration rate ml/min/1.73 m2	74.3±19.7
Chronic kidney disease classification:	
Classes 1–2	2815 (77.9)
Class 3	753 (20.8)
Classes 4–5	45 (1.2)
Active endocarditis	19 (0.5)
Neurological dysfunction	47 (1.3)
Myocardial infarction<3 months	698 (19.3)
Previous cardiac surgery	158 (4.4)
LVEF>50%	2430 (67.3)
30–50%	1043 (28.9)
<30%	140 (3.9)
Nitrates infusion at OR arrival	397 (11.0)
Critical preoperative status	65 (1.8)
Systolic pulmonary a. pressure>60 mmHg	83 (2.3)
Emergency operation	186 (5.1)
Postinfarct ventricular septal rupture	9 (0.2)
Surgery on the thoracic aorta	56 (1.5)
Additive EuroSCORE	4.8±3.1
Logistic EuroSCORE (%)	5.9±8.4
Type of operation:	
Isolated CABG	2750 (76.1)
CABG + ventriculoplasty	15 (0.4)
CABG + AVR	245 (6.8)
CABG + MV surgery	72 (2.0)
CABG + double valve surgery	20 (0.6)
CABG + triple valve surgery	3 (0.1)
CABG + other major cardiac procedures	9 (0.2)
CABG + other non cardiac procedures	13 (0.4)

	No. (%)
Isolated AVR	235 (6.5)
Isolated MV surgery ± ASD closure	127 (3.5)
Double valve surgery	24 (0.7)
Triple valve surgery	7 (0.2)
Bentall-DeBono procedure ± CABG	50 (1.4)
Other aortic procedures	2 (0.1)
Tricuspid valve surgery + other procedures	3 (0.1)
Isolated ASD closure	20 (0.6)
Isolated VSD closure	4 (0.2)
Other major cardiac procedures	8 (0.2)
Isolated major cardiac procedures	3152 (87.2)
Procedures other than isolated CABG	850 (23.5)

Continuous variables are reported as the mean±standard deviation; CABG: coronary artery bypass grafting; AVR: aortic valve replacement; MV: mitral valve; ASD: atrial septal defect; VSD: ventricular septal defect.

and ventricular septal defect). Surgery for cardiac tumours was considered as one type of major cardiac procedure. However, operations for arrhythmias or pericardial diseases were not classified as major cardiac procedures.

Study VI

This study included a series of 4,014 adult patients undergoing cardiac surgery at the Heart Center of Tampere University Hospital, Tampere, Finland, from January 2004 to December 2008. The aim of this study was to validate the modified EuroSCORE developed in Study V. Patients undergoing isolated minor procedures such as pericardiectomy or for arrhythmias were likewise excluded. No attempt was made to replace missing values. Clinical characteristics and operative data on these patients are summarized in Table 11.

Variables were classified according to EuroSCORE criteria (Roques et al. 1999) and other criteria defined in Study V. Patients were considered at high operative risk if their logistic score was within the 90th percentile of each risk algorithm as proposed by Dewey et al.(Dewey et al. 2008).

Table 11. Clinical characteristics of patients undergoing adult cardiac surgery from 2004 to 2008 at the Heart Center, Tampere University Hospital, Finland.

	No. (%)
Age (years)	66.0±10.6
Females	1041 (25.9)
Pulmonary disease	312 (7.8)
Extracardiac arteriopathy	518 (12.9)
Serum creatinine>200 micromol/l	64 (1.6)
Active endocarditis	69 (1.7)
Neurological dysfunction	165 (4.1)
Myocardial infarction<3 months	1159 (28.9)
Previous cardiac surgery	178 (4.4)
LVEF>50%	3023 (75.3)
30–50%	869 (21.6)
<30%	122 (3.0)
Nitrates infusion at OR arrival	533 (13.3)
Critical preoperative status	244 (6.1)
Systolic pulmonary a. pressure>60 mmHg	255 (6.4)
Emergency operation	667 (16.6)
Postinfarct ventricular septal rupture	7 (0.2)
Surgery on the thoracic aorta	183 (4.6)
Additive EuroSCORE	5.5±3.6
Logistic EuroSCORE (%)	8.0±11.5
Additive modified score	3.5±1.7
Logistic modified score (%)	2.2±6.1
Type of operation:	
Isolated CABG	2829 (70.5)
Isolated AVR	345 (8.6)
Isolated MV surgery	243 (6.1)
CABG + AVR	208 (5.2)
CABG + MV surgery	77 (1.9)
Any operation on the ascending aorta with any associated procedure	123 (3.1)
Triple valve surgery	2 (0.0)
Other major cardiac procedures	187 (4.7)

Continuous variables are reported as the mean±standard deviation; CABG: coronary artery bypass grafting; AVR: aortic valve replacement; MV: mitral valve; ASD: atrial septal defect; VSD: ventricular septal defect.

Anaesthesia method

The anaesthesia method consisted of combined general anaesthesia. Thoracic epidural anaesthesia was used in Studies I–IV at the discretion of the anaesthesiologist for patients with anticipated pulmonary or other significant risk. Fentanyl 3–3.5 ug/kg, and propofol 0.8–2 mg/kg were administered intravenously for anaesthesia induction, followed by continuous infusion of propofol 1–2 mg/kg/h. Pancuronium 0.10 mg/kg was administered for muscle relaxation. Clonidine 1.5–2ug/kg was administered as a slow intravenous bolus dose at induction of anaesthesia to patients without thoracic epidural anesthesia. Patients were ventilated with oxygen in air, FiO2 0.4–0.5, supplemented with isoflurane or sevoflurane.

Cardiopulmonary bypass techniques

For CPB we used a membrane oxygenator (Dideco Compactflo; Dideco S.p.A., Mirandola, Italy) with a nonpulsatile pump flow by means of a Stöckert roller pump (CAPS or SIII, Stöckert GMBH, Munich, Germany) and a systemic temperature drift down to 32–34 °C. A 40μm arterial line filter (D734, Dideco S.p.A.) was included in the CPB circuit. From 1996 to 2002 we used conventional non-coated PVC-tubings, but from 2002 we routinely used a phosphorylcholine-coated bypass circuit (Ph.I.S.I.O., Dideco S.p.A.). A blood cardioplegia technique was employed for cardiac protection in all cases. Cardiac arrest was initiated with a bolus dose of K/Mg-cardioplegia concentrate solution given in a 35 to 37 °C warm mixture of a moderately hyperkalemic 5% glucose solution and oxygenated blood infused into the aortic root in a ratio of 1:8. The mixture was cooled to about 30 °C after cardiac arrest and thereafter given as a continuous ante/retrograde infusion directly into the coronary ostia and/or through the coronary sinus, and into the venous grafts. Before declamping of the aorta the blood cardioplegia was warmed to 35 to 37 °C and infused for 4 to 5 minutes. The target activated clotting time was ≥ 600 sec due to use of a moderate dose of aprotinin (2.5–4 million units/patient).

Surgical techniques

Surgery was undertaken via full median sternotomy. In Study I all procedures were prosthetic valve implantations. Valve type was chosen in consensus with the patient, the usual dividing point between mechanical and biological valve being 70 years. In Study II, 1,604 patients were operated on with conventional CABG technique, whereas 274 (14.4%) were operated on with beating heart surgery technique.

Epiaortic ultrasound was performed in most of patients undergoing CABG. The decision to avoid aortic cross- or side-clamping was based on intraoperative findings of diseased ascending aorta and individual operative risk. A Heartstring anastomosis seal device (Guidant Corporation, San Jose, CA, USA) was used whenever a severely calcified ascending aorta prevented its safe cross- and side-clamping.

Statistical analysis

Statistical analysis was performed using SPSS statistical software (SPSS v. 14.0.1, SPSS Inc., Chicago, Ill., USA). No attempt was made to replace missing values. Continuous variables are reported as mean±standard deviations. Pearson's test, Fisher's exact test with or without the Monte Carlo method, the Mann-Whitney test and Kruskall-Wallis' test were used for univariate analysis. Receiver operating characteristics (ROC) curve was used to estimate the predictive value of continuous variables. The best cutoff values were chosen according to the best sensitivity, specificity, accuracy as well as unadjusted odds ratio. Spearman's test was used to estimate the correlation of continuous variables. Logistic regression and Cox regression analysis with the help of backward selection were used for multivariate analysis. Variables with $p<0.05$ in univariate analysis were included in the regression model. A value of $p<0.05$ was considered statistically significant.

In Study III, since patients aged ≥ 80 years had an operative risk markedly higher than that of younger patients – as indicated by EuroSCORE and Higgins score - which can be only partly explained by the age factor, we calculated a propensity score to obtain one-to-one match pairs with similar clinical and operative characteristics (other than age). Indeed, elderly patients were operated on employing less frequently one or two bilateral mammary artery grafts. Logistic regression with backward selection was performed to calculate the propensity score. All variables but age, EuroSCORE and Higgins score listed in Table 2 with a $p<0.20$ were included in the regression model. ROC curve analysis was used to estimate the area under the curve of the calculated propensity score. The latter was employed for one-to-one matching according to the difference in the propensity score <0.005.

In Study V additive and logistic scoring systems were then developed, the former having been calculated by adding rounded odds ratios. The predictive value of these risk scoring methods was evaluated in Study VI.

Long-term outcome was assessed by Kaplan-Meier's test and Cox regression analysis. Only variables with $p<0.20$ were included in the regression models for prediction of late outcome. A value of $p<0.05$ was considered statistically significant.

6 RESULTS

Study I

Spirometry parameters

Patients undergoing AVR with CABG had similar spirometry parameters to patients undergoing isolated AVR. The percentage of the predicted FVC (rho: 0.125, p=0.009) and the percentage of the predicted FEV1 (rho: 0.113, p=0.012) correlated with the preoperative left ventricular ejection fraction. Similarly, these parameters were associated with EuroSCORE left ventricular ejection fraction classes (p=0.005 and p=0.05 respectively). Interestingly, left ventricular ejection fraction <50% was significantly associated with the percentage of the predicted FVC<80% (30.6% vs. 15.5%, p<0.0001), but not the percentage of the predicted FVE1<75% (24.7% vs. 18.1%, p=0.11).

As expected, the percentages of the predicted FEV1, but not the percentages of the predicted FVC (p=0.11, and p=0.097 respectively), were significantly lower among patients with history of smoking (74.7±16.8% vs. 84.3±18.1%, p<0.0001) and current smokers (69.9±13.6% vs. 82.8±18.3%, p<0.0001).

Percentages of the predicted FVC and FEV1 did not correlate with CPB time.

Pulmonary disease and in–hospital mortality

Table 12 summarizes the immediate outcome endpoints. When all variables listed in Table 1 with a p<0.05 in the univariate analysis were included in the regression analysis, the percentages of the predicted FVC (O.R. 0.952, 95%C.I. 0.914–0.990, p=0.019), unstable angina pectoris (O.R. 12.981, 95%C.I. 1.618–104.126, p=0.016)

Table 12. Postoperative outcome after aortic valve replacement surgery.

Clinical endpoints	No. (%)
In-hospital mortality	13 (3)
30-day mortality	12 (3)
Resternotomy	48 (10)
Mediastinitis	3 (1)
Stroke	16 (4)
Stroke or TIA	20 (4)
Intra-aortic balloon pump	7 (2)
Acute renal failure requiring dialysis	2 (1)
Delirium	47 (10)
Atrial fibrillation	245 (54)
Extubation time (hours)	8±17
Reintubation	21 (5)
Pneumonia	35 (8)
Intensive care unit stay (days)	2±3
Intensive care unit stay ≥5 days	28 (6)

and CPB duration (O.R. 1.010, 95%CI 1.004–1.102, p=0.001) were independent predictors of in-hospital mortality. These variables remained independent predictors even when logistic EuroSCORE was included in the logistic regression analysis.

The percentage of the predicted FVC (AUC 0.749, 95%C.I. 0.632–0.866, p=0.002) and the percentage of the predicted FEV1 (AUC 0.723, 95%C.I. 0.591–0.854, p=0.003) had satisfactory areas under the ROC curve. The best cutoff value for the percentage of the predicted FVC was 80% (in-hospital mortality 6.3% vs. 1.3%, p=0.005, O.R. 5.100, 95%C.I. 1.544–16.849, specificity 69%, sensitivity 69%) and for the percentage of the predicted FEV1 was 75% (in-hospital mortality 5.2% vs. 1.7%, p=0.04, O.R. 3.233, 95%C.I. 1.039–10.056, specificity 67%, sensitivity 62%). History of pulmonary disease was also associated with increased risk of

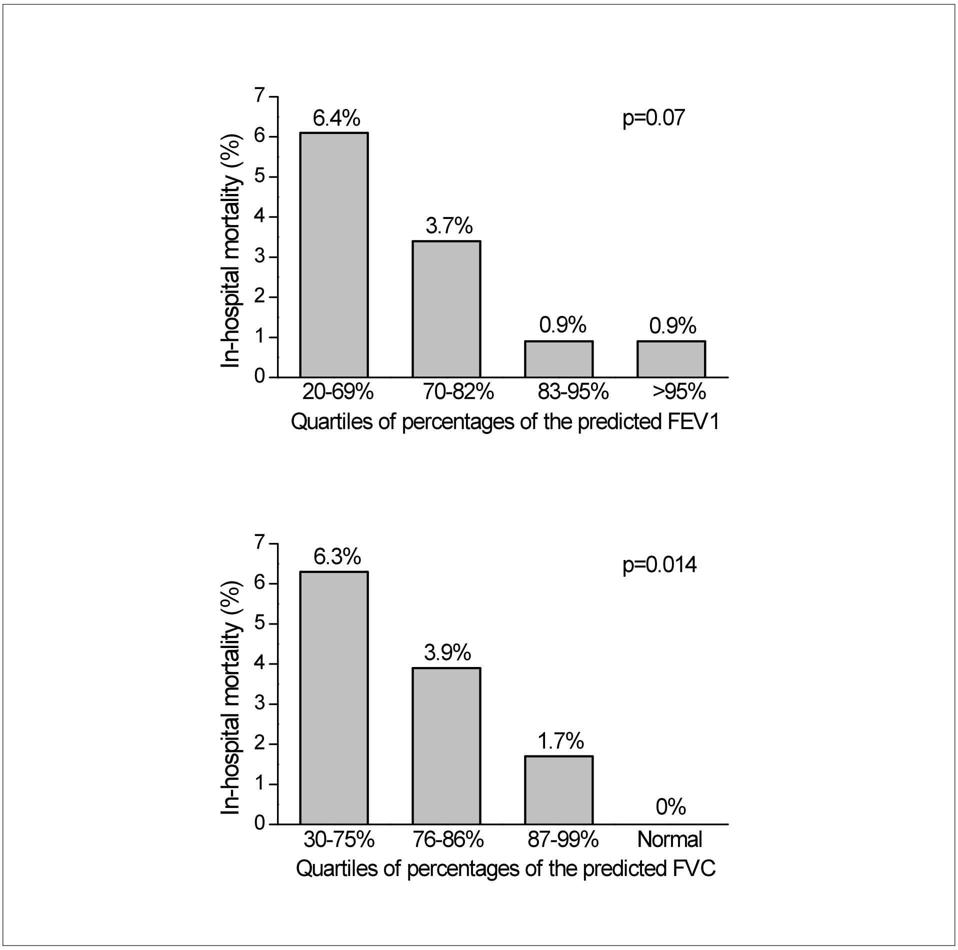


Figure 3. Observed in-hospital mortality rates after aortic valve replacement according to quartiles of percentages of the predicted FVC and of the predicted FEV1.

in-hospital mortality (9.7% vs. 1.8%, O.R. 5.893, 95%C.I. 1.911–18.167, p=0.004). However, even when the percentage of the predicted FVC<80% and the percentage of the predicted FEV1<75% were included in the regression analysis, again only the percentage of the predicted FVC was an independent predictor of adverse outcome. The mortality rates of different quartiles of percentages of the predicted FVC and FVE1 are shown in Figure 3.

Impact of pulmonary disease on the other outcome end-points

The percentage of the predicted FVC was significantly associated with postoperative stroke ($p=0.008$), but neither the percentage of the predicted FEV1 ($p=0.21$) nor history of pulmonary disease ($p=0.25$) were associated with this complication. When adjusted for cerebrovascular disease, neurological dysfunction, redo-surgery, CPB time and aortic cross-clamping time, which were significantly associated with postoperative stroke at univariate analysis, only the percentage of the predicted FVC, however, was found to be an independent predictor of stroke (O.R. 0.956, 95%C.I. 0.923–0.989, $p=0.009$). A percentage of the predicted FVC<80% was associated with a risk of postoperative stroke of 6.9% versus 1.9% among those patients with better FVC values (O.R. 3.769, 95%1.342–10.581, $p=0.012$). Stroke rates for increasing quartiles of the percentage of the predicted FVC were 1.6%, 1.7%. 3.9% and 7.1% ($p=0.10$) respectively. Similarly, the percentage of the predicted FVC was significantly associated with stroke and/or transient ischaemic attacks (Mann-Whitney test: $p=0.008$; for 80% cut-off value: 8.3% vs. 2.6%, $p=0.006$, O.R. 3.420, 95%C.I. 1.366–8.536, $p=0.006$).

Interestingly, the percentage of the predicted FVC, the percentage of the predicted FEV1 and history of pulmonary disease were not associated with postoperative pneumonia, which was otherwise significantly associated with extracardiac arteriopathy ($p=0.025$), CPB time ($p=0.004$) and aortic cross-clamping time (<0.0001).

The percentage of the predicted FVC (rho: -0.139, $p=0.003$) and the percentage of the predicted FEV1 (rho: -0.093, $p=0.050$) were negatively correlated with extubation time, but the correlation coefficients were rather small. Only the percentage of the predicted FVC correlated with length of stay in the intensive care unit (rho: -0.127, $p=0.007$). The percentage of the predicted FVC<80% (10.4% vs. 4.2%, O.R. 2.648, 95%C.I. 1.225–5.724, $p=0.011$) and history of pulmonary disease (13.1% vs. 5.1%, O.R. 2.808, 95%C.I. 1.117–6.694, $p=0.016$) were significantly associated with higher risk of intensive care unit stay ≥5days.

Study II

Pulmonary disease and immediate postoperative outcome after isolated CABG

The in-hospital mortality after isolated CABG was 1.6 % (29/1848). The percentage of the predicted FVC (AUC 0.660, 95%C.I. 0.563–0.757, p=0.003) and the percentage of the predicted FEV1 (AUC 0.636, 95%C.I. 0.527–0.745, p=0.012) were associated with in-hospital death. The lowest quintiles of percentages of the predicted FVC were associated with increased in-hospital mortality rates (2.4%, 2.8%, 1.5%, 0.3%, 0.8% respectively, p=0.036). Similarly, the lowest quintiles of percentages of the predicted FEV1 were also associated with increased in-hospital mortality rates (3.1%. 1.4%, 1.7%, 0.8%, 0.9% respectively, p=0.11), but the differences failed to reach statistical significance.

GOLD classes of percentages of the predicted FEV1 were associated with increased in-hospital mortality rates (I: 1.2%, II: 1.8%, III: 6.5%, and IV: 0% respectively, p=0.010). GOLD classes of percentages of the predicted FEV1 were associated with increased risk of combined adverse event endpoint (3.9%, 9.8%, 17.7% and 16.7% respectively, p<0.0001), stroke (1.7%, 3.4%, 3.2% and 0% respectively, p=0.059), need for intra-aortic balloon pump (0.4%, 1.1%, 3.2% and 0% respectively, p=0.097), need for postoperative de novo dialysis (0.4%, 1.7%, 1.6%, 0% respectively, p=0.016), neuropsychological disturbances (7.6%, 13.1%, 11.3% and 0% respectively, p=0.002), atrial fibrillation (36.8%, 44.4%, 46.7% and 50.0% respectively, p=0.008) as well as length of stay in the intensive care unit ≥ 5 days (1.8%, 6.0%, 9.7% and 16.7% respectively, p<0.0001).

The percentages of the predicted FVC < 70% were associated with higher rates of in-hospital mortality (2.8% vs. 1.2%, p=0.11), combined adverse endpoint (13.3% vs. 5.6%, p<0.0001), need for intra-aortic balloon pump (2.4% vs. 0.5%, p=0.016), need for postoperative de novo dialysis (2.8% vs. 0.6%, p=0.006), neuropsychological disturbances (12.4% vs. 9.3%, p=0.15), atrial fibrillation (47.1% vs. 39.0%, p=0.026), pneumonia (11.4% vs. 4.6%, p<0.0001) as well as length of stay in the intensive care unit ≥ 5 days (8.6% vs. 2.9%, p<0.0001).

The percentages of the predicted FEV1 < 70% were associated with increased risk of in-hospital mortality (3.1% vs. 1.2%, p=0.011), combined adverse endpoint (12.0% vs. 5.2%, p<0.0001), need for intra-aortic balloon pump (1.9% vs. 0.5%, p=0.004), need for postoperative de novo dialysis (2.2% vs. 0.5%, p=0.006), neuropsychological disturbances (13.7% vs. 8.7%, p=0.004), atrial fibrillation (48.0% vs. 37.9%, p=0.001), pneumonia (9.2% vs. 4.4%, p<0.0001) as well as length of stay in the intensive care unit ≥ 5 days (7.8% vs. 2.6%, p<0.0001).

Pulmonary disease defined according to EuroSCORE criteria was also associated with higher rates of in-hospital postoperative mortality (3.6% vs. 1.3%, p=0.011), combined adverse endpoint (11.6% vs. 5.8%, p=0.001), need for intra-aortic balloon pump (2.2% vs. 0.6%, p=0.007), as well as length of stay in the intensive care unit ≥ 5 days (7.6% vs. 3.2%, p=0.001). Similar trends were seen for postoperative de novo dialysis (1.3% vs. 0.8%, p=0.43), neuropsychological disturbances (11.2% vs. 9.4%, p=0.40), and atrial fibrillation (43.3% vs. 39.4%, p=0.28).

ROC curve analysis showed that FEV1 (AUC 0.626, 95%C.I. 0.517–0.734, p=0.047) and FVC (AUC 0.642, 95%C.I. 0.533–0.751, p=0.025) were significantly associated with the risk of postoperative mediastinitis.

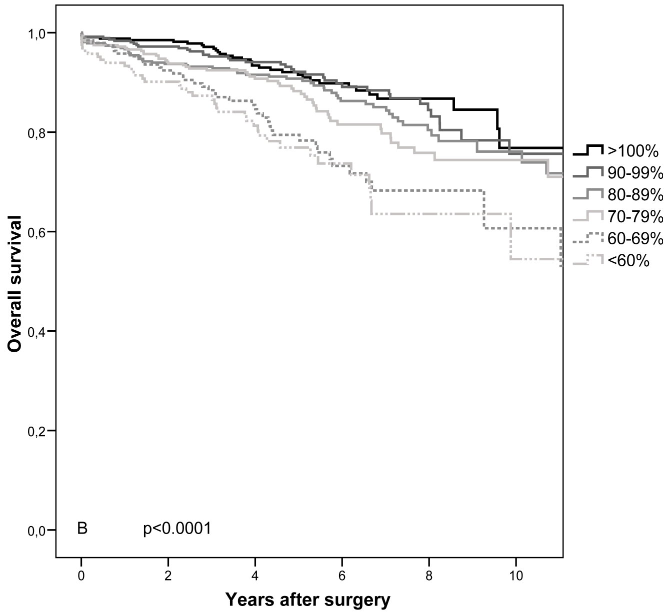
Logistic regression showed that the percentage of predicted FVC was an independent predictor of in-hospital mortality along with estimated glomerular filtration rate, age and extracardiac arteriopathy.

Pulmonary disease and late mortality

Ten-year overall survival in this series was 72.9% (119 patients entering the interval, S.E. 0.02).

Cox regression analysis showed that pulmonary disease defined according to EuroSCORE criteria and percentages of predicted FVC were among the independent predictors of late overall mortality. The percentage of predicted FEV1 was not an independent predictor of late mortality.

Since we observed that the risk of late mortality increased markedly when percentages of predicted FEV1 and FVC were lower than 70% (Figure 4), these cutoff values were included in the Cox regression model instead of their continuous val-



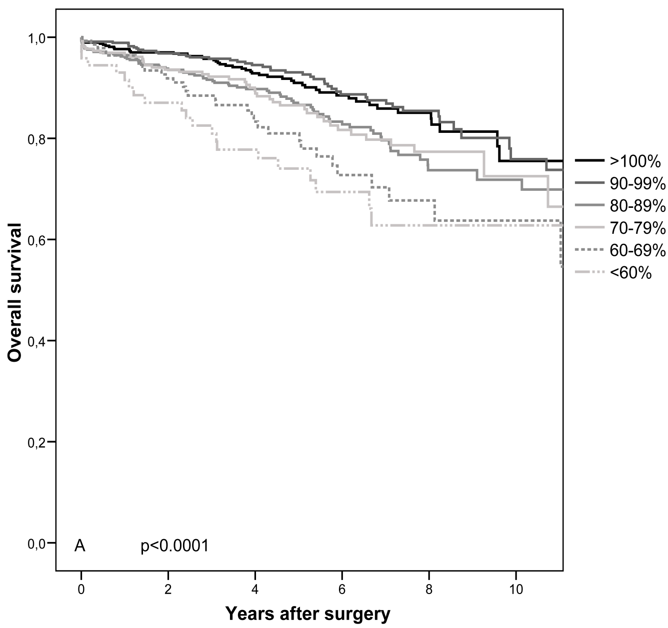


Figure 4. Kaplan Meier's estimates of overall survival rates according to different percentages of predicted FVC (A) and percentages of predicted FEV1 (B).

ues. Again, the percentage of predicted FVC < 70% (at 10 years: 63.8% vs. 74.3%, p=0.014, RR 1.50, 95%C.I. 1.08–2.08) along with pulmonary disease (at 10 years: 58.0% vs. 76.0%, p<0.0001, RR 1.75, 95%C.I. 1.29–2.39), but not percentage of predicted FEV1 < 70% were independent predictors of late overall mortality.

Study III

The prevalence of octogenarians in the cardiac surgery population has significantly increased over the years (p<0.0001, Figure 5), reaching a rate of about 15% during the last years of our experience. The increasing prevalence of octogenarians was also associated with a trend for increased 30-day mortality (1994–1998: 0% 0/23

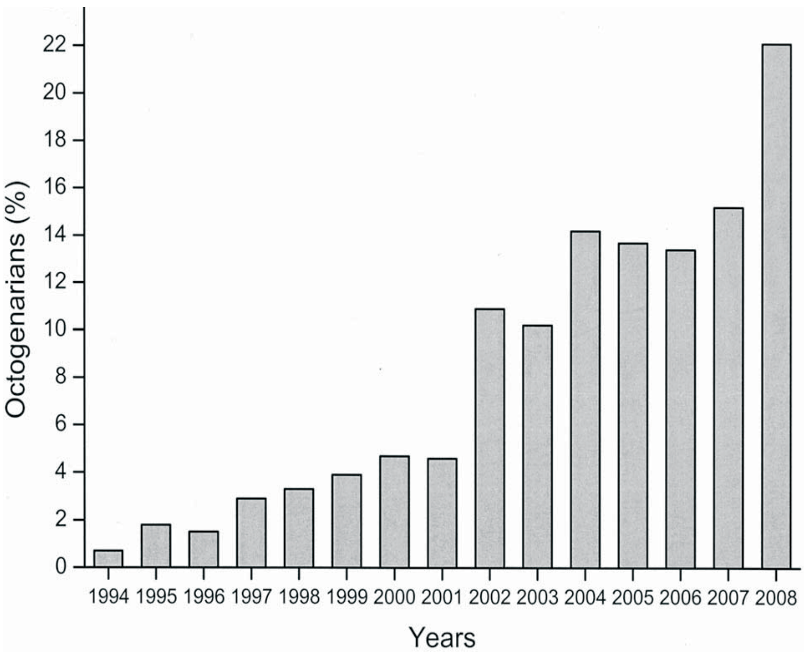


Figure 5. Increasing prevalence across the study period of patients aged 80 years or more who underwent isolated coronary artery bypass surgery at Vaasa Central Hospital, Finland (Fisher exact test, Monte Carlo method: p<0.0001).

patients; 1999–2003: 4.5%, 4/88 patients; 2004–2008: 5.5%, 9/163, p=0.75). However, this was likely due to a certain increase in the operative risk observed during the last decade (mean logistic EuroSCORE: 8.0%, 10.8% and 10.9% respectively, Kruskall-Wallis test: p=0.48) as well as a more confident and aggressive revascularization policy in this patient population.

Table 13 summarizes the postoperative complications as well as immediate and long-term outcome. Octogenarians have a significantly poorer immediate and long-term outcome than younger patients. However, when compared with pooled survival estimates according to the study by McKellar and colleagues (McKellar 2008), the overall survival of octogenarians in the present series was much better than estimated (Figure 6). This comparison could anyway, be affected by the inclusion in this systematic review of patients operated on their eighties.

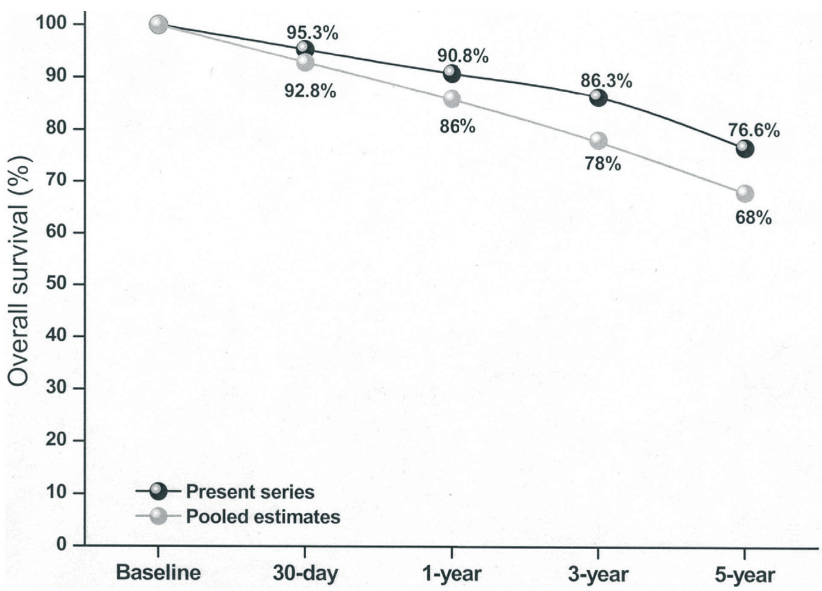


Figure 6. Overall survival rates of patients aged 80 years or more who underwent isolated coronary artery bypass surgery in the present series (black circles) and according to pooled estimates (grey circles) reported by McKellar and colleagues (McKellar 2008).

Predictors of immediate and late mortality among octogenarians

Univariate analysis showed that diabetes (9.5% vs. 3.3%, p=0.04) and critical preoperative status (50.0% vs. 3.7%, p=0.002) were the only preoperative variables predicting 30-day postoperative mortality. Logistic regression analysis showed that only critical preoperative status was independently associated with 30-day postoperative mortality (p<0.0001, OR 26.03, 95%CI 4.38–154.65).

Univariate analysis showed that diabetes (p<0.0001), extracardiac arteriopathy (p=0.006), neurological dysfunction (p=0.005), renal failure (p=0.02), critical preoperative status (p<0.0001), unstable angina pectoris (p=.004), and recent myocardial infarction (p=0.001) were associated with poorer long-term outcome.

Cox regression analysis showed that recent myocardial infarction (p=0.04, RR 1.70, 95%CI 1.04–2.79), extracardiac arteriopathy (p=0.001, RR 2.78, 95%CI 1.50–5.15), neurological dysfunction (p=0.03, RR 3.83, 95%CI 1.15–12.68), diabetes (p<0.0001, RR 2.63, 95%CI 1.61–4.30), and critical preoperative status (p<0.0001, RR 11.78, 95%CI 4.30–32.21) were independent predictors of late mortality.

Propensity score analysis

Propensity score analysis provided a model with a Hosmer-Lemeshow's p=0.32 and showed that the prevalence of female gender, recent myocardial infarction, at least one internal mammary artery graft used, bilateral mammary artery grafting and beating heart surgery significantly differed between patients aged ≥80 years and younger patients. The propensity score obtained had an area under the ROC curve of 0.71 (95%CI 0.69–0.75, p<0.0001). This propensity score provided 273 matched pairs with similar risk factors other than age.

The immediate outcome of propensity score matched pairs is summarised in Table 13. These findings demonstrate that, despite the evident negative prognostic impact of increased age, the immediate outcome of octogenarians does not significantly differ from that of younger patients with otherwise similar baseline risk factors and operated on with the same technical approach, i.e. beating heart surgery and use of internal mammary artery grafts. Figure 7 also shows the 5-year overall survival which, despite the statistical significance, is not remarkably lower than that of propensity matched patients aged < 80 years (77.0% vs. 81.3%, p=0.009).

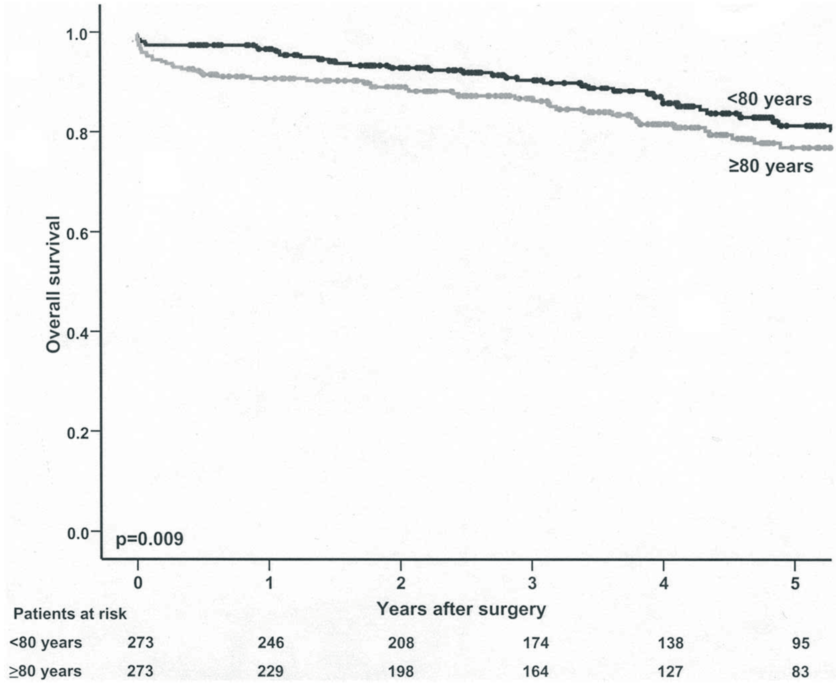


Figure 7. Overall survival rates of 273 propensity score-matched pairs of patients aged 80 years or more and less than 80 years who underwent isolated coronary artery bypass surgery (log-rank: p= 0.009).

The decrease in the survival of octogenarians seems to be evident during the first few months after surgery, but not later on (Fig. 7). Ten-year survival, given the finite nature of life, was in any case rather poor (Table 13).

Propensity score analysis, despite a rather good matching of patients, has not eliminated those patients who had prior cardiac surgery. When the latter were excluded, 5-year overall survival rates were 77.0% among octogenarians vs. 80.5% among patients aging < 80 years (p=0.019).

Table 13. Immediate and late outcome after isolated coronary artery bypass surgery in octogenarians and younger patients.

	Overall series			Propensity score matched pairs		
	Octo-genarians	Younger patients	p-value	Octo-genarians	Younger patients	p-value
	274 patients (%)	3200 patients (%)		273 patients (%)	273 patients (%)	
Immediate postoperative outcome:						
30-day mortality	13 (4.7)	40 (1.3)	<0.0001	13 (4.8)	7 (2.6)	0.17
Reoperation	18 (6.6)	161 (5.0)	0.27	18 (6.6)	20 (7.3)	0.74
Reoperation for bleeding	9 (3.3)	106 (3.3)	0.99	9 (3.3)	16 (5.9)	0.22
Stroke	7 (2.4)	7 (2.6)	0.88	7 (2.6)	6 (2.2)	0.78
Intra-aortic balloon pump	6 (2.2)	26 (0.8)	0.02	6 (2.2)	5 (1.8)	0.76
Acute renal failure requiring dialysis	7 (2.6)	28 (0.9)	0.008	7 (2.6)	3 (1.1)	0.34
ICU-stay (days)	2.0±2.7	1.6±3.5	<0.0001	2.0±2.7	1.9±3.2	0.21
ICU-stay≥5 days	24 (8.8)	121 (3.8)	<0.0001	24 (8.8)	19 (7.0)	0.43
Delirium	52 (19.0)	254 (8.0)	<0.0001	52 (19.1)	30 (11.1)	0.009
Pneumonia	21 (7.7)	177 (5.5)	0.14	21 (7.7)	18 (6.6)	0.62
Atrial fibrillation	143 (55.4)	1142 (36.5)	<0.0001	142 (55.3)	113 (43.6)	0.008
Combined adverse end-points	36 (13.1)	211 (6.6)	<0.0001	36 (13.2)	29 (10.6)	0.36
Late postoperative outcome:			<0.0001			0.009
1-year overall survival	90.8%	97.3%		90.8%	96.7%	
3-year overall survival	86.3%	93.9%		86.7%	90.5%	
5-year overall survival	76.6%	90.4%		77.0%	81.3%	
10-year overall survival	34.9%	76.1%		35.0%	55.3%	

a: In-hospital mortality, stroke, length of stay in ICU ≥5 days, acute renal failure requiring dialysis;
ICU: Intensive care unit. Values in parentheses are percentages;
Late survival has been estimated by the Kaplan-Meier's method with the log-rank test.

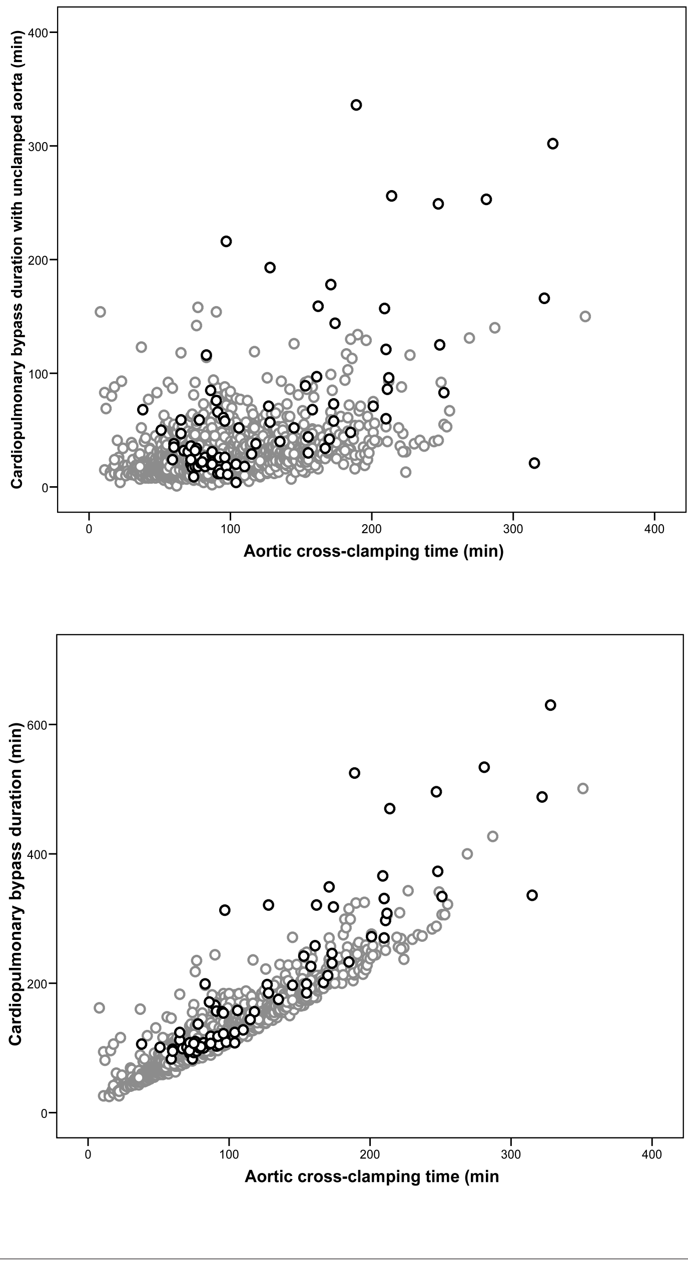


Figure 8. Aortic cross-clamping time correlated strongly with cardiopulmonary bypass duration (rho: 0.941, p<0.0001). The correlation between aortic cross-clamping time and cardiopulmonary bypass duration with unclamped aorta was somewhat weaker (rho: 0.439, p<0.0001). Black circles indicate patients who died during 30-day postoperative period.

Study IV

Aortic cross-clamping and cardiopulmonary bypass time

XCT, as expected, correlated strongly with CPBT (rho: 0.94, p<0.0001). However, the correlation between XCT and CPBT with unclamped aorta was somewhat weaker (rho: 0.44, p<0.0001). Figure 8 shows a scattered correlation indicating that prolonged XCT was not necessarily associated with prolonged CPBT with unclamped aorta.

Thirty-day postoperative mortality

Thirty-day postoperative mortality rate was 2.5% (83/3280). Additive EuroSCORE (p<0.0001, area under the curve, AUC 0.837, 95%C.I. 0.791–0.882) and logistic EuroSCORE (p<0.0001, AUC 0.84, 95%C.I. 0.80–0.89) performed well in predicting 30-day postoperative mortality.

Thirty-day mortality rate was not significantly different after isolated coronary artery bypass surgery (1.6%), isolated aortic valve surgery (1.7%) and isolated mitral valve surgery (1.7%) (p=0.75). On the other hand, 30-day mortality rates after isolated procedure, double procedure and three to four procedures were 1.7% (47/2820), 5.4% (22/404) and 25% (14/56) respectively (p<0.0001). Accordingly, the XCT (83±26 min, 134±36 min and 191±56 min respectively, p<0.0001) and CPBT (106±34 min, 173±52 min and 262±98 min respectively, p<0.0001) also correlated with the complexity of the operation.

ROC curve analysis showed that XCT (p<0.0001, AUC: 0.66, 95%C.I. 0.60–0.73), CPBT (p<0.0001, AUC: 0.73, 95%C.I. 0.67–0.78), and CPBT with unclamped aorta (p<0.0001, AUC: 0.77, 95%C.I. 0.71–0.83) were associated with 30-day postoperative mortality. The increasing risk of 30-day mortality along with increased XCT and CPBT is presented in Figure 9.

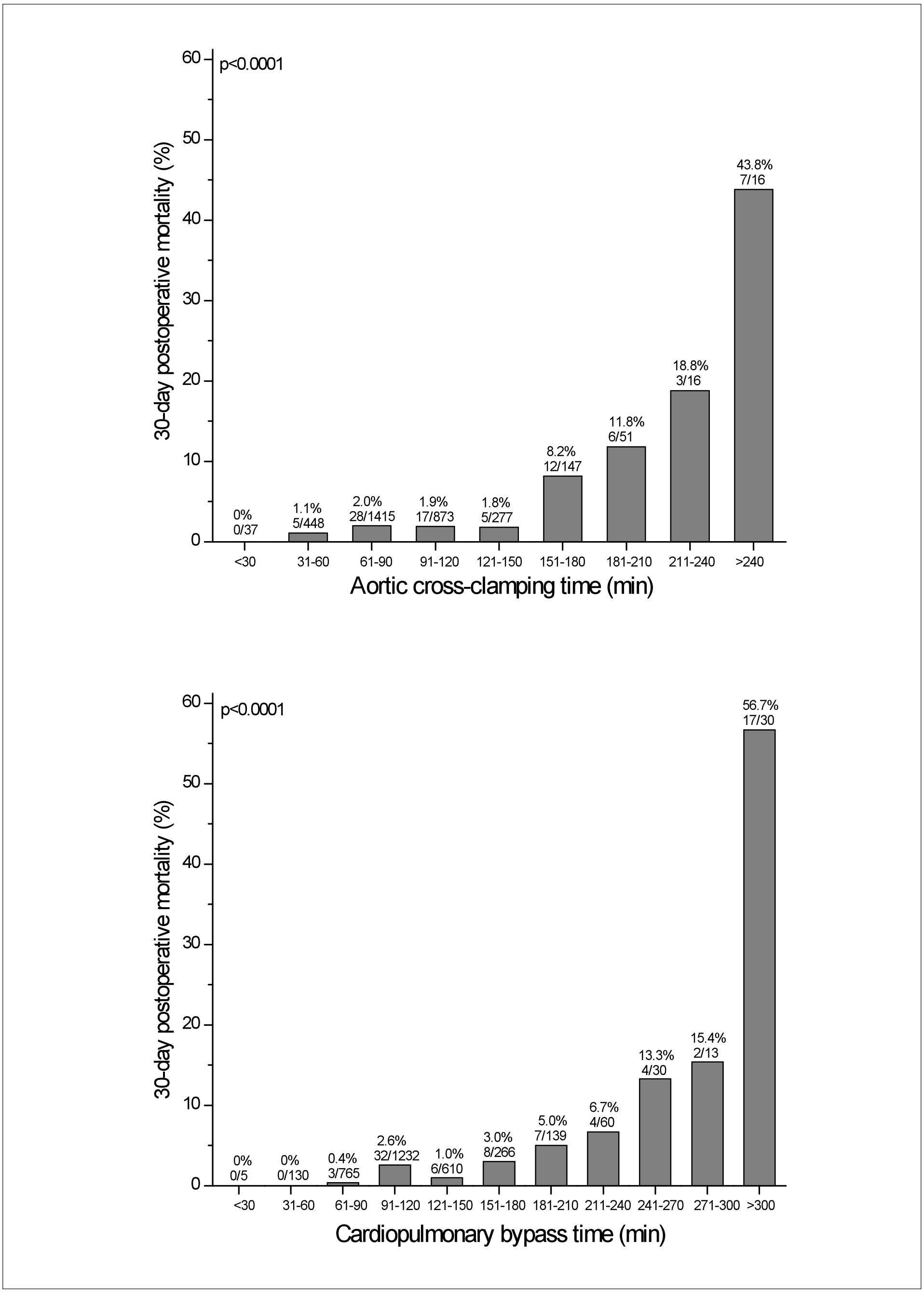


Figure 9. 30-day mortality rates for increasing duration of aortic cross-clamping ($p<0.0001$, O.R. 1.41, 95%C.I. 1.23–1.62 when adjusted for additive EuroSCORE) and cardiopulmonary bypass ($p<0.0001$, O.R. 1.45, 95%C.I. 1.30–1.61 when adjusted for additive EuroSCORE).

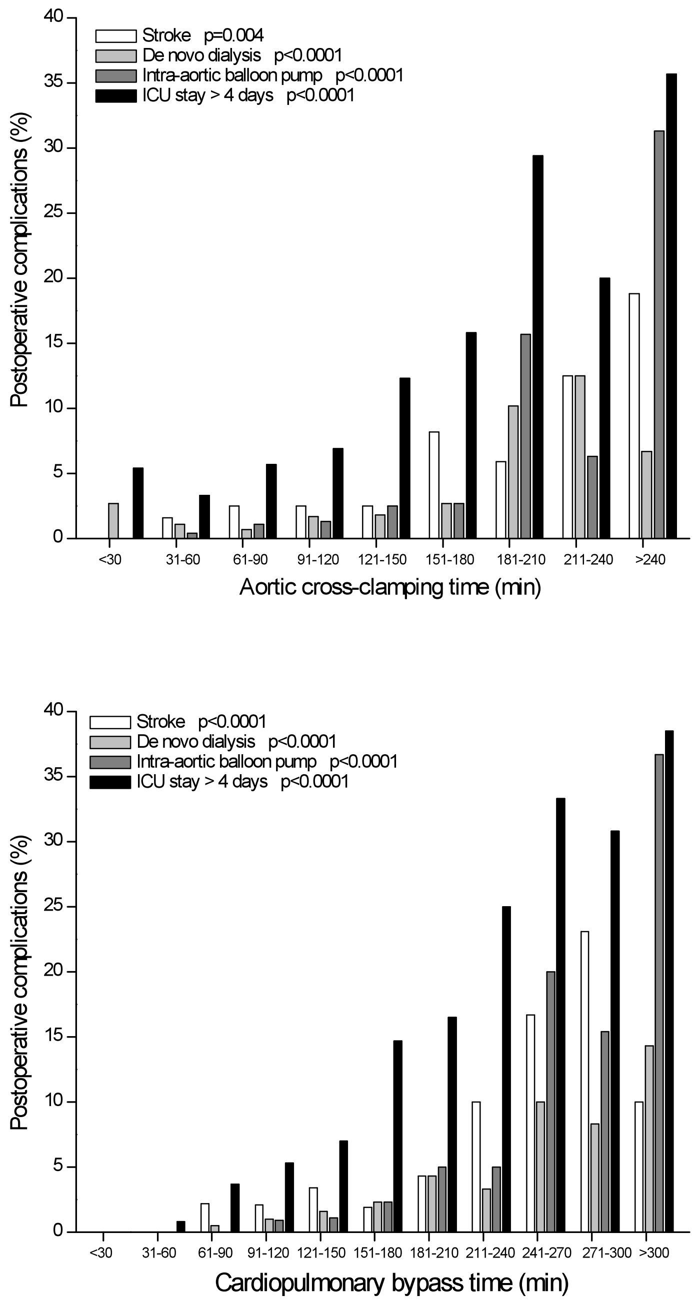


Figure 10. Rates of postoperative complications for increasing duration of aortic cross-clamping and cardiopulmonary bypass. P-values adjusted for additive EuroSCORE.

Logistic regression showed that both XCT and CPBT were independent predictors of immediate postoperative death. It is worth noting that in the correlation matrix XCT and CPBT were negatively correlated. Thus, XCT and CPBT were included in the regression model separately and the results were similar. XCT of increasing 30-minute intervals ($p=0.04$, O.R. 1.24, 95%C.I. 1.01–1.52, Hosmer-Lemeshow's test: $p=0.43$, change in -2 Log likelihood: 4.45) and CPBT of increasing 30-minute intervals ($p<0.0001$, O.R. 1.47, 95%C.I. 1.270–1.71, Hosmer-Lemeshow's test: $p=0.49$, change in -2 Log likelihood: 24.28) were independent predictors of 30-day postoperative mortality also when included separately in the regression model.

The best cutoff value for XCT was 150 min (1.8% vs. 12.2%, $p<0.0001$, O.R. 3.07, 95%C.I. 1.48–6.39 as adjusted for additive EuroSCORE and complexity of the operation; sensitivity 33.7%, specificity 93%, accuracy 91.5%) and for CPBT 240 min (1.9% vs. 31.5%, $p<0.0001$, O.R. 8.78, 95%C.I. 4.64–16.61 as adjusted for additive EuroSCORE and complexity of the operation; sensitivity 27.8%, specificity 97.8%, accuracy 96.0%).

Outcome prediction after isolated procedures

According to the logistic regression CPBT, but not XCT, was associated with 30-day mortality among patients undergoing isolated procedures. However, the area under the ROC curve of CPBT was rather small ($p=0.001$, AUC: 0.64, 95%C.I. 0.58–0.71) compared to that of the overall series and of patients undergoing complex procedures.

Outcome prediction after complex procedures

Four-hundred and twenty patients underwent two or more procedures on coronary arteries, heart valves, ascending aorta/aortic arch, atrial or ventricular septum. ROC curve analysis showed that XCT ($p<0.0001$, AUC: 0.681, 95%C.I. 0.57–0.80), CPBT ($p<0.0001$, AUC: 0.74, 95%C.I. 0.64–0.85), and CPBT with unclamped aorta ($p<0.0001$, AUC: 0.79, 95%C.I. 0.70–0.88) were associated with 30-day postoperative mortality.

When adjusted for additive EuroSCORE, XCT ($p<0.0001$, O.R. 1.01, 95%C.I. 1.01–1.02) and CPBT ($p<0.0001$, O.R. 1.01, 95%C.I. 1.01–1.02) were independent predictors of 30-day mortality among patients undergoing complex procedures. XCT >150 min (14.5% vs. 3.8%, $p<0.0001$, O.R. 4.24, 95%C.I. 2.03–8.85) and CPBT >240 min ($p<0.0001$, O.R. 9.10, 95%C.I. 4.40–18.81) were associated with greatly increased risk of 30-day mortality. When their best cutoff values were adjusted for additive EuroSCORE, XCT>150 min ($p=0.001$, O.R. 4.13, 95%C.I. 1.82–9.37) and CPBT>240 min ($p<0.0001$, O.R. 4.81, 95%C.I. 2.13–10.86) were also associated with 30-day mortality in this high risk group. The effect of combining the cutoff values of these two risk factors is shown in Figure 11 ($p<0.0001$ adjusted for additive EuroSCORE).

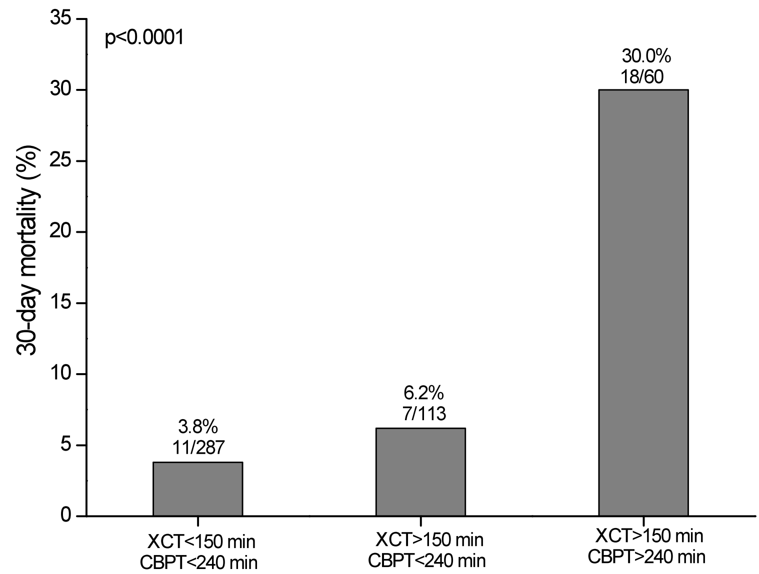


Figure 11. 30-day mortality rates after complex cardiac surgery according to different combinations of cutoff values of aortic cross-clamping and cardiopulmonary bypass duration. P-value adjusted for additive EuroSCORE. XCT: aortic cross-clamping time. CPBT: cardiopulmonary bypass time.

Severe postoperative complications

The rate of combined severe complications endpoint (30-day mortality, intensive care unit stay ≥ 5 days, stroke, postoperative use of IABP, and need for postoperative dialysis) was 10.9% (357/3280 patients). ROC curve analysis showed that XCT (p<0.0001, AUC: 0.644, 95%C.I. 0.61–0.68), CPB duration (p<0.0001, AUC: 0.70, 95%C.I. 0.67–0.73), and CPB duration with unclamped aorta (p<0.0001, AUC: 0.74, 95%C.I. 0.71–0.77) were associated with combined severe complications endpoint. Figure 11 shows the rates of severe complications according to different XCTs and CPBTs adjusted for additive EuroSCORE.

XCT correlated significantly with the number of transfused red blood cell units (rho: 0.26, p<0.0001), the number of transfused homologous blood products (rho: 0.27, p<0.0001), time to extubation (rho: 0.136, p<0.0001) and length of stay in the intensive care unit (rho: 0.19, p<0.0001). Likewise, CPBT correlated significantly with the number of transfused red blood cell units (rho: 0.31, p<0.0001), the number of transfused homologous blood products (rho: 0.32, p<0.0001), time to extubation (rho: 0.16, p<0.0001) and length of stay in the intensive care unit (rho: 0.25, p<0.0001).

Study V

Thirty-day postoperative mortality

The overall 30-day postoperative mortality rate was 2.5% (90/3613). Thirty-day postoperative mortality was not significantly different after isolated coronary artery bypass surgery (1.6%), isolated aortic valve surgery (1.7%) and isolated mitral valve surgery (2.5%) (p=0.75). On the other hand, 30-day mortality rates after isolated procedure, double procedure and three to four procedures were 1.7% (54/3152), 5.4% (22/405) and 25% (14/56) respectively (p<0.0001). Accordingly the CPB duration correlated with the numbert of procedures (106±34 min, 172±52 min and 262±98 min respectively, p<0.0001).

The area under the ROC curve for predicting 30-day mortality was much larger for estimated preoperative glomerular filtration rate (0.716, 95%C.I. 0.656–0.776, p<0.0001) than for preoperative serum creatinine (0.660, 95%C.I. 0.594–0.727, p<0.0001). Thirty-day mortality rate for CKD classes 1–2 was 1.3%, for class 3 6.1%, and for classes 4–5 13.3% respectively (p<0.0001), whereas it was respectively 12.2% and 2.4% for patients with and without renal failure according to EuroSCORE criteria (p=0.003). Estimated glomerular filtration rate, but not preoperative creatinine, was an independent predictor of 30-day mortality.

Patients' age in all regression models was an independent predictor of 30-day mortality. When we evaluated age according to additive EuroSCORE criteria, a marked difference in mortality was detected for patients aged 70 or more. However, a further increase was observed among octogenarians. Because of this, we divided patients' ages into four classes (30-day mortality rates: <60 years, 0.6%; 60–69.9 years, 1.8%; 70–79.9 years, 3.6%; ≥80 years, 4.6%, p<0.0001).

Risk factors associated with 30-day postoperative mortality in the regression analysis are listed in Table 14. The Hosmer-Lemeshow chi-square of the final regression model was 4.952, p=0.763.

ROC analysis showed that the modified score had a slightly larger area under the curve (additive: 0.867, 95%C.I. 0.830–0.904; logistic: 0.873, 95%C.I. 0.837–0.909) than the EuroSCORE (additive: 0.835, 95%C.I. 0.790–0.879; logistic: 0.840, 95%C.I. 0.796–0.883) (Figure 12) for prediction of 30-day postoperative mortality. Similar areas under the ROC curve were observed in predicting in-hospital mortality (area under the ROC curve: additive modified score 0.867, 95%C.I. 0.832–0.902; logistic modified score 0.872, 95%C.I. 0.838–0.907; additive EuroSCORE 0.831, 95%C.I. 0.788–0.873; logistic EuroSCORE 0.836, 95%C.I. 0.794–0.878).

Table 14. Results of logistic regression in predicting 30-day postoperative mortality and additive score points as estimated in Study V.

	Beta-coefficient	Standard error	p-value	Odds ratio	95% interval confidence	Additive score points
Patients' age						
<60 years			0.005			
60–69 years	0.779	0.571	0.173	2.178	0.711–6.674	2
70–79 years	1.371	0.550	0.013	3.940	1.340–11.588	4
≥80 years	1.853	0.606	0.002	6.377	1.944–20.923	6
Female	0.536	0.263	0.042	1.709	1.020–2.863	2
Pulmonary disease	1.080	0.280	0.000	2.945	1.700–5.101	3
Extracardiac arteriopathy	0.778	0.320	0.015	2.178	1.164–4.075	2
Neurological dysfunction	1.461	0.615	0.018	4.309	1.290–14.398	4
Redo surgery	1.049	0.385	0.006	2.855	1.343–6.070	3
Critical preoperative status	2.079	0.371	0.000	7.993	3.860–16.552	8
Left ventricular ejection fraction						
>50%			0.001			
30–50%	0.870	0.262	0.001	2.387	1.429–3.986	2
<30%	1.102	0.461	0.017	3.010	1.218–7.436	3
Surgery of the thoracic aorta	2.115	0.549	0.000	8.287	2.825–24.305	8
Ventricular septal defect secondary to myocardial infarction	2.219	0.777	0.004	9.197	2.005–42.192	9
Chronic kidney disease classification						
Classes 1–2			0.000			
Class 3	0.995	0.263	0.000	2.704	1.615–4.527	3
Classes 4–5	1.858	0.586	0.002	6.413	2.035–20.211	6
Number of procedures						
1			0.000			
2	0.736	0.306	0.016	2.089	1.146–3.807	2
3–4	1.882	0.489	0.000	6.567	2.516–17.139	7
Constant	-6.779	0.567	0.000	0.001		

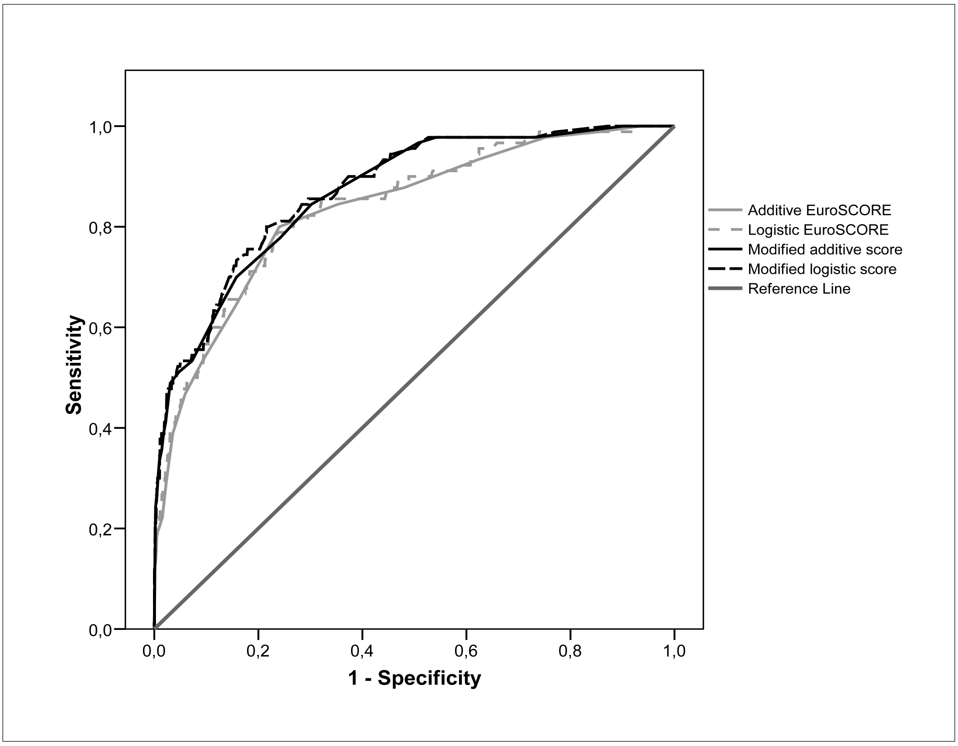


Figure 12. Receiver operating characteristics curves of additive and logistic EuroSCORE and modified score in predicting 30-day postoperative mortality after adult cardiac surgery.

Such marginal superiority of the modified score shown by ROC analysis became much more evident when we compared observed and predicted 30-day mortality along different additive scores. In fact, EuroSCORE was associated with a major difference between predicted and observed mortality, whereas the modified score provided predicted mortality rates much closer to those observed (Figure 13).

Outcome prediction after isolated major procedures

The modified risk score performed somewhat better than EuroSCORE in predicting 30-day mortality after isolated coronary artery bypass surgery (area under the ROC curve: additive modified score 0.818, 95%C.I. 0.759–0.876; logistic modi-

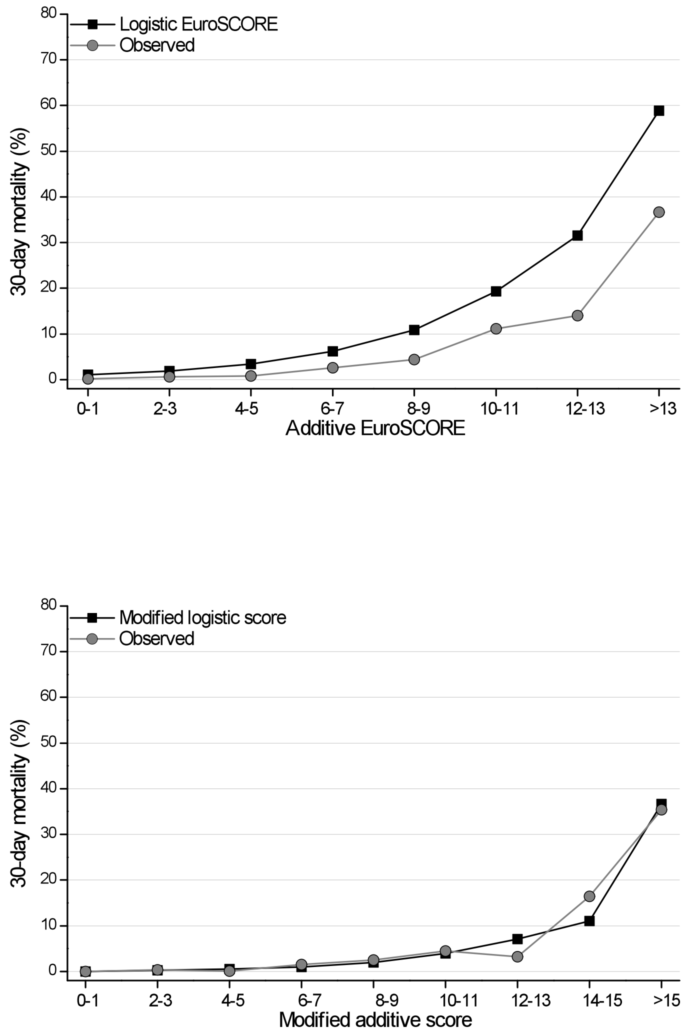


Figure 13. Observed and predicted postoperative mortality according to the logistic EuroSCORE and the logistic modified score in different additive modified score classes and additive EuroSCORE classes.

fied score 0.819, 95%C.I. 0.761–0.877; additive EuroSCORE 0.781, 95%C.I. 0.710–0.853; logistic EuroSCORE 0.785, 95%C.I. 0.714–0.855).

The modified risk score as well as EuroSCORE performed extremely well in predicting 30-day mortality after isolated aortic valve surgery (area under the ROC curve: additive modified score 0.946, 95%C.I. 0.898–0.993; logistic modified score 0.964, 95%C.I. 0.932–0.997; additive EuroSCORE 0.908, 95%C.I. 0.844–0.971; logistic EuroSCORE 0.936, 95%C.I. 0.893–0.980). When both additive scores were divided into quartiles, mortality occurred only in the last quartiles, i.e. additive scores ≥ 8 (EuroSCORE: observed 30-day mortality 8.2%, mean expected mortality 15.9±9.9%; modified score: observed 30-day mortality, 6.6%, mean predicted mortality 5.3±6.9%).

The modified risk score also performed well in predicting 30-day mortality after mitral valve surgery (area under the ROC curve: additive modified score 0.877, 95%C.I. 0.805–0.950; logistic modified score 0.907, 95%C.I. 0.850–0.964). EuroSCORE tended likewise to be a valid predictor of postoperative mortality after isolated mitral valve surgery (area under the ROC curve: additive EuroSCORE 0.801, 95%C.I. 0.505–1.096; logistic EuroSCORE 0.832, 95%C.I. 0.605–1.058).

Severe postoperative complications

Combined adverse end-point (30-day mortality, intensive care unit stay ≥ 5 days, stroke, postoperative use of intra-aortic balloon pump, and need for postoperative dialysis) was observed in 383 patients (10.6%). Both risk scoring methods were good predictors of combined end-point (area under the ROC curve: additive modified score 0.782, 95%C.I. 0.760–0.807; logistic modified score 0.786, 95%C.I. 0.762–0.810; additive EuroSCORE 0.748, 95%C.I. 0.722–0.774; logistic EuroSCORE 0.752, 95%C.I. 0.726–0.778).

Long-term outcome

The modified score had a somewhat better area under the ROC curve (additive: 0.841, 95%C.I. 0.810–0.872; logistic: 0.849, 95%C.I. 0.818–0.879) tan the EuroSCORE (additive: 0.807, 95%C.I. 0.771–0.844; logistic: 0.815, 95%C.I. 0.780–0.851) in predicting overall mortality at 1 year.

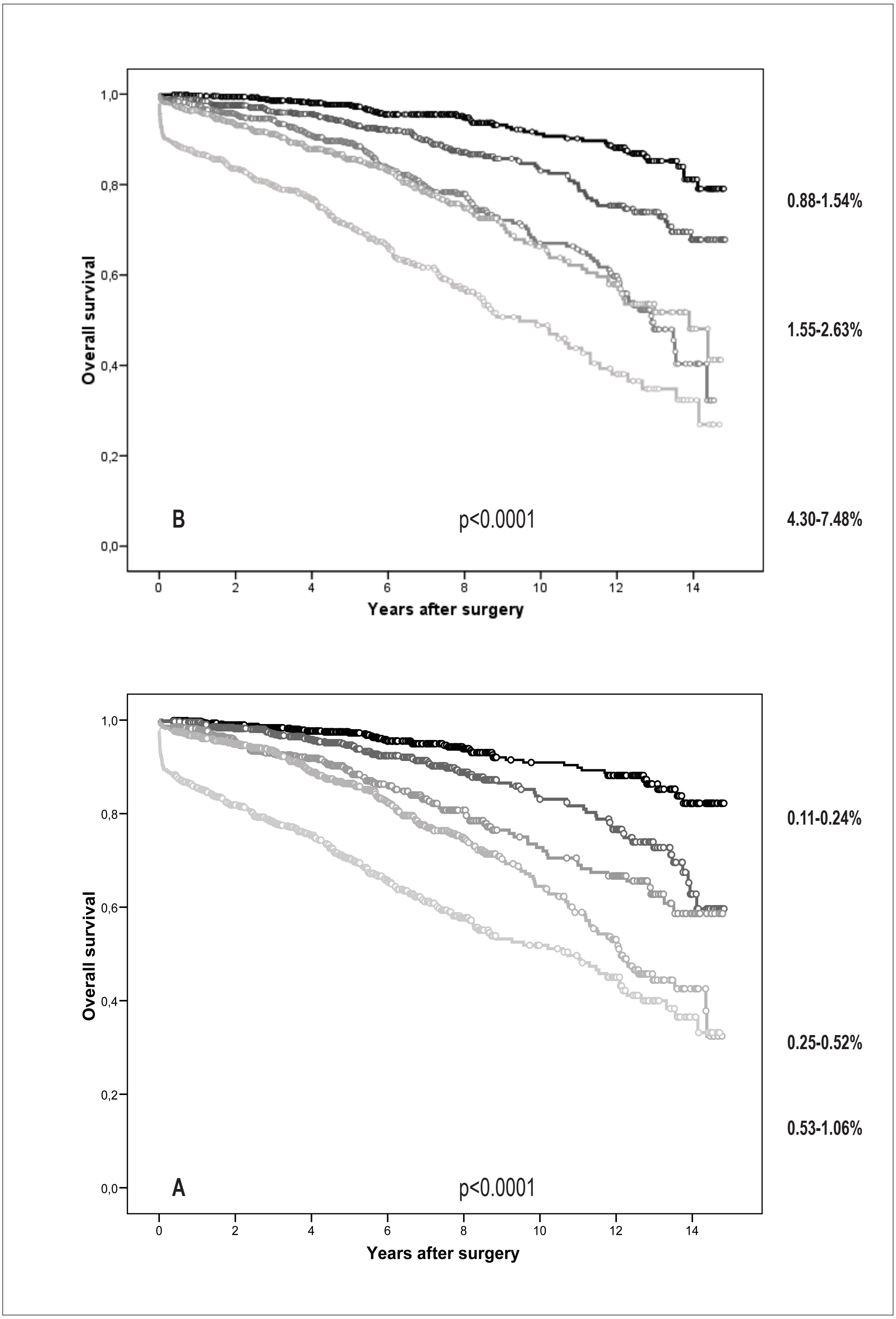


Figure 14. Kaplan-Meier estimates of overall survival after adult cardiac surgery according to quintiles of logistic modified score (A) and logistic EuroSCORE (B).

According to Cox's survival analysis, both scoring methods were good predictors of all-cause late mortality (when both scoring methods were included in the regression analysis: additive modified score, R.R. 1.132, 95%C.I. 1.099–1.167; additive EuroSCORE, R.R. 1.091, 95%C.I. 1.055–1.129). Similar results were obtained when only operative survivors were included in the analysis. Figure 14 shows the Kaplan-Meier estimates of overall survival according to logistic modified score and the logistic EuroSCORE quintiles.

Study VI

In-hospital postoperative mortality rate was 3.2% (129/4014). Stroke occurred in 1.9%, low cardiac output syndrome in 4.0% and renal complications in 2.3% of these patients. Both EuroSCORE (AUC for additive EuroSCORE 0.81, 95%C.I. 0.78–0.85, AUC for logistic EuroSCORE 0.82, 95%C.I. 0.79–0.85) and modified score (AUC for additive modified score 0.79, 95%C.I. 0.75–0.83, AUC for logistic modified score 0.79, 95%C.I. 0.75–0.83) performed well in predicting in-hospital mortality in this series (Fig. 15). These scoring methods were also predictors of postoperative stroke (logistic EuroSCORE: AUC 0.72, 95%C.I 0.67–0.77; logistic modified score: AUC 0.71, 95%C.I. 0.66–0.77), renal complications (logistic EuroSCORE: AUC 0.79, 95%C.I 0.74–0.84; logistic modified score: AUC 0.78, 95%C.I. 0.74–0.83), and low cardiac output syndrome (logistic EuroSCORE: AUC 0.81, 95%C.I 0.77–0.84; logistic modified score: AUC 0.76, 95%C.I. 0.72–0.80).

The mean logistic EuroSCORE was 8.0±11.5% and the mean logistic modified score was 2.2±6.1%. Thus the observed to expected ratio for in-hospital mortality was 0.4 for logistic EuroSCORE and 1.5 for logistic modified score. The expected mortality rates as estimated by the logistic EuroSCORE and the logistic modified EuroSCORE are presented in Figure 16 along with increasing classes of additive scores with their related observed in-hospital mortality rates.

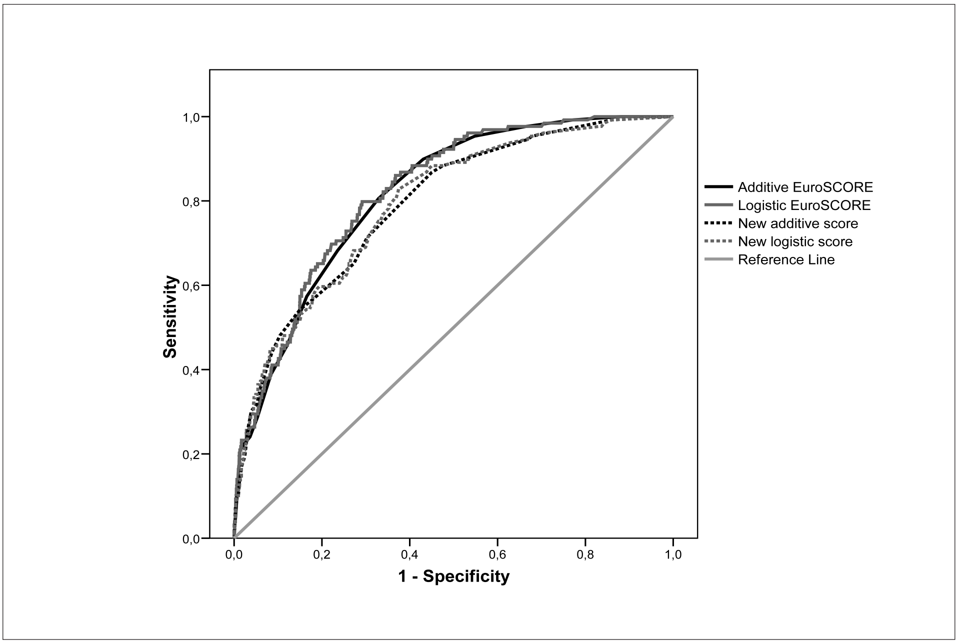


Figure 15. Receiver operating characteristics curves of additive and logistic EuroSCORE and modified score in predicting in-hospital mortality after adult cardiac surgery in patients included in Study VI.

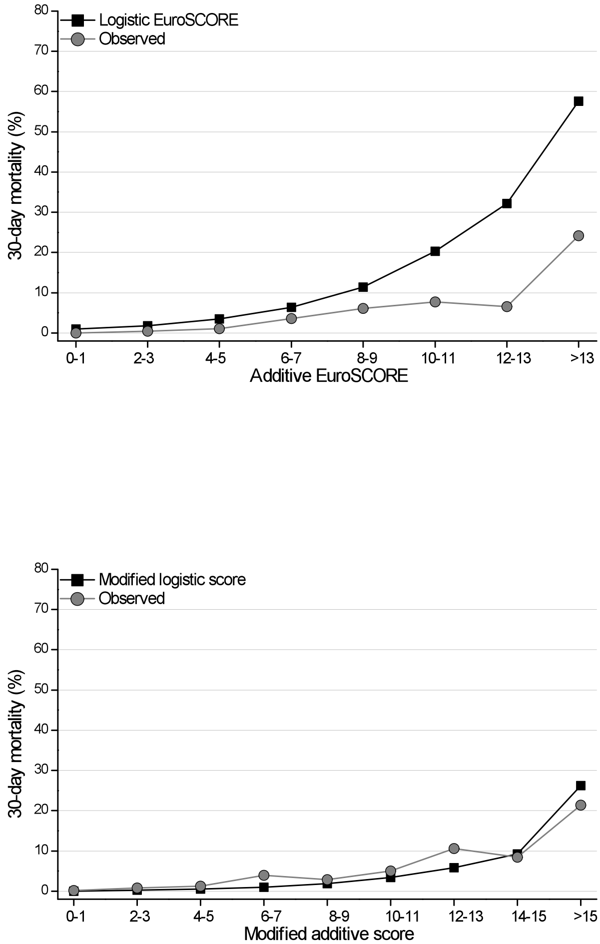


Figure 16. Observed and predicted postoperative mortality according to the logistic EuroSCORE and the logistic modified score in different additive modified score classes and additive EuroSCORE classes.

The observed to predicted ratio in high-risk patients (within the 90th percentile of each risk algorithm) was 0.36 (13.2%/36.2% in 402 patients) for logistic EuroSCORE, whereas it was 0.99 (14.7%/14.9% in 395 patients) for logistic modified score. This indicates that the latter score predicted the in-hospital mortality of these high risk patients almost perfectly.

Figure 17 shows the observed and predicted mortality rates in patients undergoing isolated coronary artery bypass grafting, isolated aortic valve replacement and isolated mitral valve surgery.

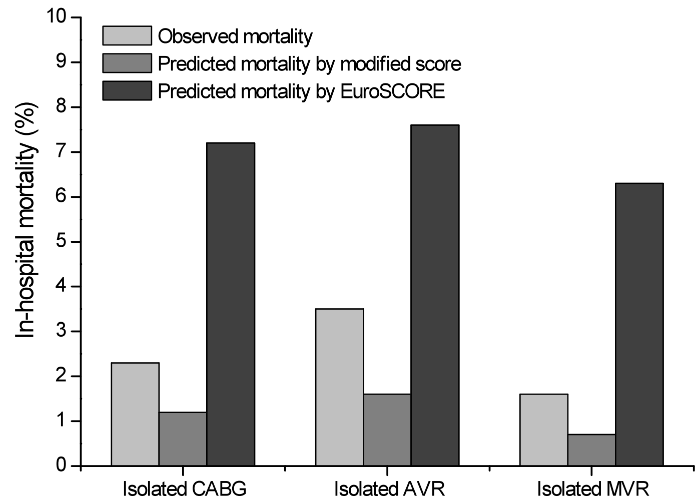


Figure 17. Observed and predicted in-hospital mortality according to the logistic EuroSCORE and the logistic modified score in patients undergoing isolated coronary artery bypass grafting (CABG), isolated aortic valve replacement (AVR) and isolated mitral valve replacement/repair (MVR).

Among 345 patients who underwent isolated aortic valve procedure, logistic EuroSCORE (AUC 0.65, 95%C.I. 0.53–0.77) and logistic modified score (AUC 0.64, 95%C.I. 0.51–0.76) had somewhat smaller areas under the ROC curve than those obtained in the overall study population. Seventy patients had a logistic EuroSCORE >10% and their observed in-hospital mortality rate was 5.7%. Their related mean logistic EuroSCORE was 20.8%, whereas their mean logistic modified score was 3.7%. The related observed to predicted ratios for logistic EuroSCORE were 0.3 and 1.5 respectively.

The observed to predicted ratio in high-risk patients (within the 90th percentile of each risk algorithm) undergoing isolated aortic valve replacement was 0.11 (2.9%/27.6% in 34 patients) for logistic EuroSCORE, whereas it was 0.44 (2.9%/6.6% in 34 patients) for logistic modified score.

7 DISCUSSION

Knowing, and controlling of risks by all means is an essential part of medical practice. Concerning surgery, recognizing the risks connected to the individual patient, his/her illness, the planned surgical procedures and postoperative circumstances is an essential part of the treatment process. Identifying the individual risks enables the best tailored treatment possible for each patient, to an accurate calculation of individualized prognosis and to plan and allocate treatment resources. Therefore it is of the utmost importance that the evaluation of risks is as accurate as possible. It is equally important to know which risks are increasing with regard to each patient in order to minimize their effects by appropriate pre-, intra- and postoperative treatment. This is rendered more difficult by rapidly evolving surgical technology and a steadily increasing proportion of ageing and sicker people in patient materials.

Within heart surgery, several risk scoring methods have been developed in recent decades. The most used algorithms predicting in-hospital mortality are the STS score, used in USA and the EuroSCORE, launched in 1999 in Europe. Both of these coprehensively screen for risk factors connected to the patient and his/her heart condition and give an estimate of the in-hospital mortality risk for a planned procedure. Where the STS score is a continuously developing risk profile, updated by several centres and a steadily growing patient database, the additional EuroSCORE is essentially based on the original material of 19.000 patients operated on over ten years ago. Later on a more powerful tool, the logistic EuroSCORE was developed to predict 30-day mortality more accurately. Especially the additive EuroSCORE but also the logistic EuroSCORE have long been known to overestimate mortality in low-risk patients and to underestimate mortality in very high-risk patients (Choong,C.K. 2009). Around the world, wide variations between different institutions have been reported (Nashef,S.A. 2009). A more accurate risk evaluation would therefore necessitate a validation of each institute. Time is also already passing the original EuroSCORE. The most complex surgical procedures and the growing significance of extracardiac diseases are underestimated. A planned procedure to update the EuroSCORE is ongoing in 2010 (Nashef,S.A. 2010).

7.1 Pulmonary function and outcome after cardiac surgery

Cardiac surgery by its very nature alters pulmonary and cardiac mechanics (Weissman 1999). The effects related to median sternotomy, use of CPB, impaired postoperative cardiac function, and manipulation of the thoracic contents contribute to postoperative derangements of the pulmonary function with deterioration of the ventilatory capacity in the immediate postoperative period. Pulmonary complications are believed to be mainly related to depressed postoperative cardiac function (Weissman 1999). In fact, postoperative low cardiac output leads to cardiogenic pulmonary oedema as well as to severe muscle fatigue with secondary poor chest mobility, ineffective coughing and lack of deep breathing. These events are further complicated by the systemic inflammatory response related to surgery and the use of cardiopulmonary bypass (Paparella et al. 2002a), the lungs being the main target of this inflammatory response. Thus, it is not unexpected that patients with poor preoperative pulmonary function could experience adverse postoperative outcome. It is therefore important to establish the impact of COPD on the postoperative outcome and to identify patients at highest risk of adverse events.

Clinically, COPD represents a broad spectrum of lung diseases often difficult to define, including emphysema, combined with various degrees of fibrosis, cystic fibrosis, bronchiectasia and components of asthma. It has both an obstructive and restrictive nature revealed with spirometry (The definition of emphysema, the report of a national heart, lung, and blood institute, division of lung diseases workshop, 1985). There is currently a proof on the systemic effects of COPD, which contribute to the poor prognosis of these patients (Agusti 2007). Several studies have established that COPD is associated with low-grade systemic inflammation, which is partly independent of smoking (Sin et al. 2004). Such a systemic inflammation is likely to be a major contributor in the pathogenesis of adverse effects of COPD including weight loss, skeletal muscle dysfunction, cardiovascular disease, depression and osteoporosis (Agusti 2007). Importantly, contrary to most of the risk factors contributing to adverse immediate and late outcome of patients undergoing adult cardiac surgery, COPD is to some extent a treatable disease. Sin and colleagues (Sin et al. 2004, Huiart et al. 2005) showed that corticosteroids significantly reduced plasma levels of C-reactive protein in these patients. Interestingly, very low dose of inhaled steroids has been shown to reduce the risk of myocardial infarction in COPD patients (Huiart,L. 2005). In the TORCH study (Towards a Revolution in COPD Health), the combined treatment with salmeterol and fluticasone reduced the risk of death by 17.5% in patients with moderate and severe COPD (Calverley et al. 2007). Furthermore, potential beneficial effects in terms of early and late survival with the use of angiotensin-converting enzyme inhibitors and statins have been reported in patients with COPD (Mancini et al. 2006, van Gestel et al. 2008). Other studies showed that preoperative pulmonary rehabilitation improves outcome after CABG (Rajendran et al. 1998, Hulzebos et al. 2006).

COPD has been considered generally by most of the operative risk scores, but its functional nature and severity have not been addressed by these models. EuroSCORE gives COPD a value of 1 point, the Cleveland score two points, taking no further consideration to the severity of this illness (Higgins et al. 1992b, Roques et al. 1999). Both evaluations are based on continuous medication, not grading of the disease. Our pulmonary function study on CABG patients (II) showed that GOLD classes of predicted FEV1 were associated with increased in-hospital mortality rates (I: 1.2%, II: 1.8%, III: 6.5%, IV: 0% respectively, p=0,010) when total in-hospital mortality in this material was 1.6%. Garcia Fuster et al. showed a similar tendency in a CABG material from Spain, where in-hospital mortality was correspondingly: I: 0.9%, II: 0.4%, III: 10.8%, IV: 54%, total in-hospital mortality being 3.1% (Fuster et al. 2006). Depending on the severity of the pulmonary dysfunction, mortality can be very high. Therefore, a correct diagnosis of COPD and its severity (by paying attention to the continuous nature of COPD) are indispensable in order to take better preoperative care of patients having diminished lung capacity (Samuels et al 1998b, Medalion et al. 2004).

Patients undergoing cardiac surgery are changing to an increasingly higher risk profile: they are older and have several comorbidities. Traditional cardiac-related risk variables such as left main stenosis and angina class are losing their predictive value in favour of extracardiac factors such as universal arteriosclerosis, chronic renal failure or COPD (Abramov et al. 2000, Grover et al. 1996, Garcia Fuster et al. 2005). Our modified EuroSCORE (V) increased the relative weight of both pulmonary and renal disorders by giving COPD 3 points (vs. 1 in EuroSCORE), and by classifying chronic renal failure as a continuous phenomenon much as COPD above.

Interestingly, in our AVR study (I) FVC, FEV1 or a history of pulmonary disease were not associated with postoperative pneumonia. On the other hand our CABG study (II) showed a clear association of FVC<70% (11.4%) and FEV1<70% (9.2%) with postoperative pneumonia. Garcia Fuster et al. had the same finding in their CABG series, where pneumonia and sepsis were particularly more frequent in moderate-severe COPD patients (18% and 11% respectively) (Garcia Fuster et al. 2005). The vulnerability of CABG patients could be associated with more vigorous manipulation of thoracic cage and increased prevalence of universal ASO (Ross 1999).

In our AVR study (I), only FVC was an independent predictor of stroke. FVC<80% was associated with a 6.9% risk of postoperative stroke vs. 1.9% among those patients with better FVC. Stroke rates for decreasing quartiles of FVC were 1.6%, 1.7%, 3.9% and 7.1% (P=0.10) respectively. In the CABG study, FEV1 had also a certain association with postoperative stroke (Gold I: 1.7%, II: 3.4%, III: 3.2%, IV: 0%, respectively, p=0.059). It has been observed that spirometric parameters could be a surrogate of extrapulmonary conditions associated with postoperative stroke. In fact, current evidence suggests that COPD itself has systemic effects which contribute to the poor prognosis of these patients (Agusti 2007). In this sense, the FEV1 and FVC values evauated here had the merit of identifying those patients with poor general conditions along with poor lung function. It is worth noting that this was independent of smoking habit.

Despite the fact that FEV1 is generally considered one of the most important parameters in the identification and staging of COPD, we observed in our CABG study (II) that FVC had a somewhat better prognostic value than FEV1. It is possible that heart failure related to coronary artery disease may have resulted in restrictive pulmonary changes (Johnson et al. 2001). This finding is supported by our AVR study (I), where we showed that low left ventricular ejection fraction correlates with FVC values more than with FEV1 values.

In our CABG patients (II) ten year overall survival was 72.9%. COPD had a significant impact on the long-term survival after isolated CABG. Patients with FVC<70% as well as those with pulmonary disease according to EuroSCORE criteria had a significant reduction of overall survival rate at 10-year of 10% to 18% respectively. This effect seems to be independent of smoking habit.

The role of OPCAB in the treatment of COPD patients has not been determined. Cox et al. in 2000 showed that myocardial revascularization with or without cardiopulmonary bypass caused a similar degree of pulmonary dysfunction, as assessed by alveolar-arterial oxygen gradient (Cox et al. 2000). They postulated that the deterioration in pulmonary gas exchange associated with cardiac surgery is due to other factors than the use of CPB. On the other hand, Güler et al., while comparing conventional cardiopulmonary bypass to OPCAB or minibypass, observed that FEV1 acquired in the second postoperative month was significantly lower than the preoperative values only in the conventional perfusion group (Güler et al. 2001). Manipulation of the beating heart and twisting into the right chest to perform posterolateral anastomosis may be a key factor for diminished lung function after OPCAB surgery. As also shown by Staton et al., compared to CABG/CPB, OPCAB was associated with a greater reduction in postoperative respiratory compliance (Staton et al. 2005). This may be in conjunction with the concomitant increased fluid requirements necessary to maintain haemodynamic stability.

Actually, mild COPD is well tolerated by both CABG and AVR patients. Moderate to severe COPD, on the contrary, is associated with several serious postoperative complications including increased in-hospital mortality rates, stroke, need for intra-aortic balloon pump, need for postoperative de novo dialysis, neuropsychological disturbances, atrial fibrillation, pneumonia, combined adverse end point and length of stay in the intensive care unit (I–II). The results of Studies I–II suggest that preoperative pulmonary function testing could be beneficial in preoperatively identifying high-risk patients. The optimization of management in the preoperative, perioperative and postoperative periods may be the key to reduce the negative outcomes in the high-risk group (Samuels et al. 1998). This is of importance in light of recent studies showing improved outcome in patients undergoing pulmonary rehabilitation before CABG (Rajendran et al., 1998Hulzebos et al. 2006). The use of thoracic epidural anaesthesia may decrease post-operative morbidity after cardiac surgery, particularly in patients with compromised pulmonary function. However, reports are contradictionary and hence the use of TEA in high-risk cardiac patients remains controversial (Royse et al. 2003, Tenenbein et al. 2008, Popping et al. 2008).

7.2 Coronary artery bypass surgery in octogenarians

In Finland the number of individuals aged 80 years or over has increased 3-fold during the past 30 years and will increase even more in future decades. There is a growing demand for health care for this aged population. Fast developing technology, including catheter-based techniques, has widened the limits of invasive care to fields where the risks and benefits so far are not established. Minimally invasive surgery has enabledt treatment options for patients who earlier were beyond known surgical care. This has happened especially to aged people with several comorbidities. Age is an important but, at the same time, a most confusing risk factor as the 'biological' variation within the same age group is greater than in younger people. On the one hand there is an octogenarian without any medication or known comorbidities, taking care of him/herself. On the other hand there is a geriatric patient with several illnesses, poor cardiac condition among them, requiring care on the ward. Selection criteria for invasive care in octogenarians have approached those in younger people, as seen in our material. Yet a number of old people are not referred to cardiac care because of lack of evidence-based criteria for invasive care (Zingone et al. 2009). This introduces a referral and selection bias among invasively treated octogenarians confusing the weight of age as a risk factor still further. Clearly, advanced age increases the operative risk.

In our evaluation of the performance of EuroSCORE (IV), we increased the weight of aged people by categorizing age classes and giving six modified points beginning from the age of 80 years. Nevertheless, the performance of patients over 80 years in our CABG study (III) is quite acceptable, also compared to other studies (30-day mortality 4.7%, 5-year survival 77%) (Alexander et al. 2000, Suojaranta-Ylinen et al. 2006, Zingone et al. 2009). The 5-year survival especially is surprisingly good, 77%, among Finnish population where life expectancy for an 80-year old man is 7.6 years and for an 80-year old woman 9.4 years. (Tilastokeskus/Statistics Finland). Contemporary literature shows an operative mortality between 2.7% and 6.4% for isolated CABG and a five-year life expectancy of 65% (Tugtekin et al. 2007, Zingone et al. 2009, Maganti et al. 2009).

A greater share of octogenarians was operated on urgently (because of recent myocardial infarction, unstable angina and critical preoperative status) compared to the younger patient group (III). This may influence the inferior primary outcome after CABG compared to the propensity score-matched younger pairs. It is proposed that earlier referral and intervention is essential to improve results in this patient population (Kirsch et al. 1998). Despite the large and expanding elderly population presenting for ACS care, available evidence is limited and insufficient to guide management in this subgroup to the same degree of certainty as in younger populations (Alexander et al. 2007).

On the other hand, in elective patients we always considered the possibilities for preoperative rehabilitation in order to diminish the risk of perioperative complications. We believe that this has a positive influence on the parallel long-term survival over five years compared to the propensity score-matched younger pairs. Also, intraoperative ultrasound was used to detect calcified aortas. Zingone et al. showed that postoperative complications were stronger risk factors for hospital deaths than preoperative comorbidities and procedural variables. Their impact on long-term survival was also significant (Zingone et al. 2009). As stated by David B. Ross in the invited commentary of this article: ”These patients will do well if the operation is meticulously performed and they can avoid complications.

Conversely, they do not recover as well as younger patients from misadventures". Therefore, especially in this subgroup of older patients, avoiding complications is the main key factor both for immediate and for long term good outcome.

The most appropriate method of revascularization for this group of patients has not been determined. McKellar et al. performed a systematic review and a meta-analysis of 66 studies of coronary revascularization in patients aged over 80 years comparing PCI vs. CABG. Thirty-day mortality and one year survival were similar (7.3% for CABG vs. 5.4% for PCI and 86% for CABG vs. 87% for PCI respectively) (McKellar et al. 2008). IMA grafting has been shown to improve primary and mid-term survival, angina and the functional class of octogenarians. Operative mortality with or without IMA grafting (5% versus 10%, p = 0.11) and midterm survival with or without IMA grafting (70% versus 56% at 4 years, p=0.21), however, was not statistically significant (Moon et al. 2001). IMA was used in 65% of cases. In our series, at least one mammary graft was used in 80.3% of cases, which also may have positively influenced long term survival.

In terms of Health Related Quality of Life (HRQoL) octogenarians are also doing well. In Fruitman's material 127 patients over 80 years old were operated on. SF-36 scores were equal to or better than those for the general population of age greater than 65 years. Of the survivors, 83.7% were living in their own homes, 74.8% rated their health as good or excellent (Fruitman et al. 1999). Jensen made a sub-study of the randomized Best Bypass Surgery Trial comparing off-pump to on-pump treatment, with respect to peri- and postoperative mortality and morbidity in patients with moderate to high-predicted preoperative risk. Both on-pump and off-pump patients improved in health-related quality of life scores after CABG surgery. No clinically relevant difference between the groups could be demonstrated (Jensen et al. 2006).

Atrial fibrillation, decline of neurocognitive functions, delirium, stroke, increased length of stay, and renal failure are common complications among elderly people. In terms of these illnesses these people could benefit from OPCAB surgery. Avoiding CPB may reduce complications and diminish mortality related to CABG in older people.(Al-Ruzzeh et al. 2006, Guru et al. 2007, Ricci et al. 2001, Angelini et al. 2009, Athanasiou et al. 2004). Seniors are known to be very sensitive to the side effects of the CPB and require increased resource utilization compared with younger patients (Scott et al. 2005). Recent literature comparing on- and off-pump techniques in elderly is scarce and reflects the difficulty of enrolling these very fragile patients in prospective randomized studies of sufficient power (Cartier 2009). Nevertheless, a few of them demonstrate the potential benefit of avoiding CPB in elderly population (Athanasiou et al. 2004, Panesar et al. 2006, Kerendi et al. 2008).

The elderly with ACS have a high risk of death and adverse events. Thereby they often have greater absolute treatment benefits than do younger patients. If cardiac surgery is increasingly carried out safely on aged people with acceptable results, the effect of cardiac intervention on subjectively experienced health related quality of life will perhaps be more important than its effect on longevity alone (Jokinen et al. 2010). The greatest improvement in HRQoL occurs in patients with the poorest preoperative cardiac-symptoms-related HRQoL, whereas patients with relatively good HRQoL derive less benefit (Rumsfeld et al. 2004). Despite the large and expanding elderly population presenting for ACS care, existing evidence is limited and insufficient to guide management in this subgroup to the same degree of certainty as in younger populations (Alexander et al. 2007).

7.3 Duration of aortic cross-clamping and cardiopulmonary bypass

Cardiopulmonary bypass time (CPBT) has been shown to be associated with enhanced systemic inflammatory response (Khabar et al. 1997, Whitten et al. 1998, Paparella et al. 2002b) and increased morbidity and mortality after pediatric and adult cardiac surgery (Kang et al. 2004, Salis et al. 2008). Our study (IV) confirms that the longer the aortic cross clamp time (XCT) and CPBT the worse their detrimental effects will be. Naturally, long XCT and CPBT reflect the complexity of the procedure and hence also the preoperative condition of the patient and the heart. When categorizing the procedures as isolated, double or a combination of three to four procedures, we saw mortality increase from 1.7 % – 5.4 % – 25 %. Accordingly, both XCT and CPBT increased 2.5-fold from simple to the most complex procedures.

Myocardial protection is of paramount importance when XCT increases. During warm blood cardioplegia, Onorati et al. found that 6.9% of their CABG patients had Troponin I greater than 3.1 μg/L at 12 hours which correlated with lower in-hospital and follow-up survival after one year and lower freedom from cardiac events. Aortic cross-clamp time greater than 90 minutes and cardiopulmonary bypass time greater than 180 minutes were independent predictors of myocardial damage in multivariate analysis (Onorati et al. 2005). The negative impact of myocardial ischaemia, long duration of cardiopulmonary bypass, technical demands of the operation and the patients individual characteristics are an entity where individual co-factors are difficult to discern. Myocardial protection has unequivocally been the same throughout our whole series, though perfusion techniques have varied somewhat within our material. With these limitations in mind we attempted to estimate the adverse effects of prolonged XCT and CPBT and observed in our material that if cardiopulmonary perfusion time is kept under 240 minutes and aortic cross clamp time under 150 minutes, cardiac surgery can be performed with a fairly low risk of postoperative mortality and morbidity, independent of the patients' operative risk and the complexity of the procedure.

Also, when adjusted for additive EuroSCORE, XCT and CPBT were independent predictors of 30-day mortality among patients who underwent complex procedures. CPBT was a much stronger predictor of 30-day mortality than XCT, which may reflect the critical condition of the patient, technical difficulties during the operation or suboptimal myocardial protection.

Our study also confirms the impact of XCT and CPBT on postoperative morbidity as shown in Figure 10. The strong correlation between postoperative stroke and XCT, and especially CPBT, is particularly interesting. CPBT has been shown by other authors to increase the risk of stroke (Hogue et al. 1999, Bucerius et al. 2003b). Bucerius, in a material of over 16,000 patients from Leipzig, showed that CPBT>2 hours was an independent risk factor for stroke. Further, Hogue in a material of nearly 3,000 patients showed that duration of cardiopulmonary bypass was independently associated with early stroke.

Both XCT and CPBT correlated significantly with the number of transfused red blood cell units, the number of transfused homologous blood products, time to extubation and length of stay in intensive care unit.

While short XCT and CPBT are associated with very low risk of postoperative adverse events, prolonged XCT and CPBT on the other hand do not automatically indicate a poor prognosis. Markedly long XCT and CPBT did not univocally result in postoperative mortality. Even in complex procedures, where XCT was >150 min, but CPBT still <240 min, the mortality rate was not higher than 6.2%. Only when XCT was >150 min and CPBT exceeded 240 minutes, did mortality rise to 30%. Noteworthy still, 70% of these high-risk patients survived. Thus although these cutoff values (XCT>150 min, CPBT>240 min) have a high accuracy (over 90%), they have a rather low sensitivity and very low predictive value in identifying poor outcomes.

7.4 Application of risk adjustment models

Outcomes frequently considered include mortality, morbidity, critical events, resource utilization, costs, functional status postoperatively, and patient satisfaction (e.g. in terms of quality of life). There are variable practices on which data should be routinely collected, how individual variables should be defined and how defined outcomes should be risk-stratified. Individual variables can be either naturally complex, poorly defined or both, such as the complexity of the operation, unstable angina, extracardiac arteriopathy and pulmonary disease (V). By accurately identifying the high-risk patient, it may be possible cost-effectively to alter and focus therapy on selected patients or patient groups and thereby reduce risk.

7.4.1 Mortality

Mortality is an outcome measure that is universally reported. The advantages of mortality as an outcome measure include lack of ambiguity and availability of mortality data from a variety of sources, including national databases. The limitations of mortality as a sole outcome measure are particularly evident in cardiac surgery, where unadjusted mortality figures can vary in a range from 2.0% to 4.5% (Higgins et al. 1992c, Edwards et al. 1994a). Mortality also does not accurately reflect costs, because early death results in a lower cost than prolonged hospitalization and treatment of various complications. Short-term mortality is thus probably not by itself an adequate indicator of resource use or quality of care.

Caution must be exercised when applying scoring systems to individual patients, because the score produces a probability of death, but the fate of an individual is binary: the patient either survives or dies. Probabilities are not predictions and scoring systems alone cannot be used to define operability because there is no level of preoperative risk that always is associated with poor outcome (Higgins 1998).

Long-term mortality, probably the most useful outcome, is rarely assessed, essentially because of the difficulty of following up patients over a long period of time. It certainly should be a priority for future research in risk modelling. (Kolh 2006). In this regard, the findings by Nilsson et al. that some risk stratification models, such as EuroSCORE, can predict 1-year mortality, are potentially important, but require further validation.(Nilsson et al. 2006)

7.4.2 Morbidity

Morbidity is a more attractive endpoint for analysis, because it constitutes the major determinant of hospital cost and quality of life after surgery. Being more frequent than mortality, it could provide more information and be measured in terms of postoperative complications and length of hospital stay. However, for most scoring models, predictive values for morbidity are considerably lower than predictive values for mortality. Various algorithms have been developed to predict postoperative renal insufficiency or failure, delayed extubation and length of stay in the ICU (Wong et al. 1999, Suematsu et al. 2000, Nilsson et al. 2004a, Mehta et al. 2006). There would also be interest in using these models for resource planning and prediction of costs.

Earlier studies have implied that preoperative risk factors may be used to predict costs of cardiac surgery (Smith et al. 1997, MaWhinney et al. 2000). The additive EuroSCORE model has good discriminatory power and accuracy for an ICU stay longer than 2 days (Nilsson et al. 2004a). It appears that patients requiring prolonged ICU stay tend to have more unstable angina, left ventricular dysfunction, pulmonary hypertension and extracardiac arteriopathy. Previous cardiac surgery and emergency operations also contribute to extended ICU stays (Messaoudi et al. 2009). Other risk factors not included in the EuroSCORE have also recently been investigated. Hypertension, atrial fibrillation, smoking, increased body mass index, diabetes and hypercholesterolemia have been shown to be strong predictors for prolonged ICU stay following cardiac surgery (Ghotkar et al. 2006, Bucerius et al. 2004). Intraoperative factors like prolonged operation and perfusion times, IABP-support and intraoperative hemofiltration are also independent predictors of prolonged ICU stay, while OPCAB and MIDCAB procedures seem to be associated with lower prevalence of prolonged ICU stay (Bucerius et al. 2004). A prolonged ICU stay is much more dependent on patient's preoperatvive characteristics and intraoperative events than a prolonged preoperative stay on the ward. Besides the costs of the operation itself, the costs of the ICU care are most dominant and a specific risk algorithm for the prediction of ICU stay would be useful, both from an economic standpoint and for rational planning of weekly resources.

Continuous development of specific morbidity risk scores could improve outcome and hospital cost prediction. Furthermore, because of the heterogeneity of morbidity events, future scoring systems should probably generate separate predictions for mortality and morbidity events.

Patient satisfaction is another outcome measure that requires substantial effort to collect, but should be highly valued by health care professionals.

7.5 Evaluation of risk scoring

Several risk scoring methods have been developed and employed during the last two decades to stratify the risk of cardiac surgical patients. Among these, the European system for cardiac operative risk evaluation (EuroSCORE) has been shown to be a fairly reliable and simple method to predict both immediate and late mortality (Biancari et al. 2006, Toumpoulis et al. 2005, Nilsson et al. 2006).

The additive EuroSCORE model has been shown to work satisfactorily to predict 30-day mortality in many European countries (Roques et al. 2000) and in the United States (Nashef et al. 2002) and compares favourably with the Society of Thoracic Surgeons' (STS) risk score (Nilsson et al. 2004b). Nilsson in 2006 compared 19 commonly used cardiac surgical risk scores with regard to their validity in a single institution patient population (Nilsson et al. 2006). The results showed that four of the algorithms had superior performance and accuracy to the other 15 algorithms in predicting 30-day and 1-year mortality. The logistic and additive EuroSCORE outperformed the rest of the algorithms, Cleveland and Magovern scales following next.

However, at least the original additive EuroSCORE model constructed in 1999 tends to overpredict the mortality risk in lower risk groups (Geissler et al. 2000, Asimakopoulos et al. 2003, Gogbashian et al. 2004b, D'Errigo et al. 2008, Brown et al. 2008). On the other hand, the additive model seems to underestimate mortality in high-risk patient groups (Roques et al. 2003a, Michel et al. 2003a, Gogbashian et al. 2004a). The later (2003) constructed logistic EuroSCORE is more accurate in predicting mortality, especially in high-risk patients (Roques et al. 2003a, Michel et al. 2003a) but requires computerized analysis. In high-performing centres and countries even the logistic EuroSCORE has a tendency to overpredict the mortality (Bhatti et al. 2006, D'Errigo et al. 2008, Yap et al. 2006, Zheng et al. 2009). In the United Kingdom cardiac surgical mortality is currently running at approximately 0.6 of EuroSCORE prediction, the Italian CABG outcome project generated a coefficient of 0.4. The same finding was made in our study (V) where, especially in high-risk groups, the logistic EuroSCORE tended to overestimate mortality. Estimation of the individual risk of patients undergoing cardiac surgery is difficult also due to the complex nature of surgical, anaesthesiologic and any related perioperative treatment. Individual comorbidities (possibly not included in risk stratification models), variations in case mixes and development of new techniques in cardiac surgery (such as catheter-based and minimally invasive techniques) further complicate precise risk analysis. Comparison between institutions is also difficult because of different case mix and various risk profiles between materials (Zheng et al. 2009, Choong et al. 2009). An institutionally corrected estimate can be made by quoting a predicted mortality = patient logistic EuroSCORE x hospital mortality / hospital logistic EuroSCORE. This coefficient gives a more realistic picture of the performance of a particular institute, also where strict universal restrictions are in place for certain operations. For example, if the criterion for including a patient for a transcatheter aortic valve operation is a calculated logistic EuroSCORE of 20%, the true limit of performance of the institute is 20% divided by the coefficient of the particular institute. However, reliance on a risk stratification model that over-predicts mortality may have serious consequences, because it leads to a false sense of confidence, underperformance may go undetected, and patient welfare may be compromised.

The environment in which cardiac surgery is performed is changing drastically. This evolution has been driven by continuously evolving surgical and anaesthetic skills, development and spread of interventional cardiology, off-pump coronary bypass surgery, catheter-based interventions and minimally invasive, robotically assisted and hybrid cardiac procedures for cardiac disease. Thus, the majority of data used to generate the existing risk stratification systems for cardiac surgery predates many of the newer surgical techniques. Patients referred for cardiac surgery nowadays have extensive coronary disease, associated valvular diseases, are older, and have a greater burden of both cardiac and non-cardiac comorbidities. What this has done and will continue to do to the outcomes of cardiac surgery is a matter of great debate and has escaped the frames of conventional risk models. At the present time it is possible to operate on patients with very poor left ventricles with EF 20%–25%. However, existing models give no extra weight for left ventricular performance <30%–40%, depending on the individual algorithm. EuroSCORE gives the same risk for an individual coming for an aortic valve operation compared to a patient scheduled for a combination of CABG and mitral valve operation, not to mention an operation including double-valve surgery combined with a CABG, which still has the same risk estimate.

7.6 Modified EuroSCORE

We attempted to modify the EuroSCORE in order to preserve all the positive aspects inherent in it. The accuracy was increased by more precise classification of some heavy risk factors such as renal and pulmonary insufficiency, and complexity of the procedure. Our study (V) confirmed that even the simplified version of the modified EuroSCORE could estimate the operative risk for cardiac surgical patients fairly accurately. This was accordingly successfully validated with cardiac surgical material from Tampere (VI). The accuracy of the modified score was particularly obvious in high-risk patients defined as those included in the 90th percentile of this algorithm. In our regression model, some EuroSCORE variables such as emergency surgery, recent myocardial infarction and nitrate-infusion on arrival in the operating theatre were not predictive of adverse outcome. This can be explained by the subjective nature and the influence of logistic factors in defining these variables. On the other hand, it reflects the diminishing weight of these conditions as risk factors, and the increasing weight of risk being loaded on various extracardiac comorbidities of the individual patient.

7.7 Future aspects of risk calculation

Of all the risk algorhitms available to day, only the STS database is continuously developing with material collected. Among other older models, EuroSCORE, developed more than 10 years ago, begins now to be out of date. Changes in patient characteristics, medical care, and the surgical and anaesthetic spectrum have exceeded the limits set by the initial EuroSCORE. This year, several units within and beyond Europe are participating in data collection aiming to derive an updated risk stratification model.

7.8 Limitations of the study

The present patient material was collected prospectively. Only EuroSCORE values were retrospectively calculated for those patients operated on before the launch of the EuroSCORE in 1999. However, the analysis of this material is retrospective. This is also a single institution database having, however, the power of homogeneity in terms of anaesthesia, surgical techniques and protection of the heart.

Another limitation of the study is the long time period of data collection and analysis (14 years); changes especially in patient population are quite evident during the study period.

8 SUMMARY AND CONCLUSIONS

These studies suggest that pulmonary disease is an important risk factor leading to markedly increased in-hospital and long-term mortality after adult cardiac surgery. Despite the fact that FEV1 is generally considered one of the most important parameters in the identification and staging of COPD, we have observed here that FVC had a somewhat greater prognostic significance than FEV1.

Immediate and five-year survival of octogenarians undergoing CABG can be better than previously expected. Survival of octogenarians may be lower during the first months after cardiac surgery, after which, during the following five years, the life expectancy may not differ much from that of younger patients with otherwise similar operative risks.

With current methods in adult cardiac surgery, cardiac procedures with aortic cross-clamp time less than 150 minutes and cardiopulmonary bypass time less than 240 minutes are associated with a fairly low risk of immediate postoperative events. It seems that long cardiopulmonary bypass time is a more important predictive factor than long aortic cross-clamp time.

Modified EuroSCORE derived from adult cardiac surgical material from Vaasa Central Hospital and validated with a material from Tampere University Hospital, proved to be a more accurate risk scoring method in the immediate postoperative period than the traditional EuroSCORE. This improvement could be achieved by modifying a few of EuroSCORE variables and distributing more weight on parameters which in the light of current knowledge are of increasing importance.

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Pulmonary Function and Immediate Outcome of Patients Undergoing Aortic Valve Replacement

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Background and aim of the study: **The study aim was to evaluate whether pulmonary function, as assessed by spirometry, affects immediate outcome after aortic valve replacement (AVR).**
Methods: **Data relating to the preoperative percentages of predicted forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1) were retrieved from a series of 453 patients who underwent AVR, with or without coronary artery bypass surgery.**
Results: **The percentage of predictive FVC (odds ratio (OR) 0.952; 95% CI 0.914-0.990; AUC 0.749; p = 0.019), but not of predicted FEV_1, nor any history of pulmonary disease, proved to be independent predictors of in-hospital mortality, even when adjusted for the logistic EuroSCORE. A percentage predictive FVC of <80% proved to be the best cut-off (in-hospital mortality 6.3% versus 1.3%; p = 0.005; OR 5.100; 95% CI 1.544-16.849; specificity 69%, sensitivity 69%). The percentage of predictive FVC was found to be an independent predictor of stroke (OR 0.956; 95% CI 0.923-0.989; p = 0.009). Patients with a percentage of predictive FVC <80% had a risk of postoperative stroke of 6.9% versus 1.9% among those patients with better FVC values (OR 3.769; 95% CI 1.342-10.581; p = 0.012). Patients with a percentage of predictive FVC <80% (10.4% versus 4.2%; OR 2.648; 95% CI 1.225-5.724; p = 0.011) and a history of pulmonary disease (13.1% versus 5.1%; OR 2.808; 95% CI 1.117-6.694; p = 0.016) had a significantly higher risk of an intensive care unit stay of five or more days. Postoperative pneumonia was not associated with either spirometric parameters, nor with any history of pulmonary disease.**
Conclusion: **Pulmonary disease, as indicated by decreased preoperative values of FVC and FEV_1, is an important comorbidity factor in patients undergoing AVR surgery. Further studies are required to demonstrate whether the identification and treatment of these patients could improve their outcome after AVR.**

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Patients with severe chronic obstructive pulmonary disease (COPD) are known to be at increased risk of mortality and morbidity (1), and this is particularly true when they undergo major surgery (2).

Although, several risk-scoring methods include pulmonary disease as a major determinant of mortality after adult cardiac surgery (3-5), the adverse role of this condition has not been recognized in many other major risk-scoring methods (6-9). Whilst COPD has been shown to predict the immediate outcome after coronary artery bypass surgery (CABG) (10,11), in patients undergoing aortic valve replacement (AVR) there is less evidence of any impact of pulmonary disease on the immediate postoperative outcome. A recent extensive systematic review of the prognostic factors in patients undergoing AVR failed to identify pulmonary disease as a risk factor for early mortality (12).

The aim of the present study was to evaluate whether pulmonary disease, as assessed by spirometry, had any impact on the immediate outcome after AVR, with or without CABG.

Clinical material and methods

Patients

A total of 453 patients who underwent spirometry immediately before AVR surgery, with or without CABG, at the Vaasa Central Hospital, Vaasa, Finland, between January 1996 and June 2008, was included in the study. Patients who underwent any other concomitant heart valve operation, as well as surgery on the ascending aorta, were excluded from the analysis.

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The patient data were collected prospectively into an institutional cardiac surgery database. Spirometry was performed preoperatively in all patients; the percentages of predicted forced vital capacity (FVC) and of predicted forced expiratory volume in 1 s (FEV_1) were calculated according to normal values of the Finnish population, as reported by Viljanen and colleagues (13).

As spirometry is performed routinely before cardiac surgery at the authors' institution, none of the patients was asked to consent to participate in the study; neither was approval sought from the Institutional ethics committee to conduct the study, as it represents a review of the authors' clinical experience.

Anesthesia

In the majority of patients a combined general anesthesia was utilized, but thoracic epidural anesthesia was used (at the discretion of the anesthesiologist) in patients with anticipated pulmonary or other significant risks. Fentanyl (3-3.5 µg/kg) and propofol (0.8-2 mg/kg) were administered intravenously to induce anesthesia, followed by a continuous infusion of propofol (1-2 mg/kg/h). Pancuronium (0.10 mg/kg) was administered as a muscle relaxant. Clonidine (1.5-2 µg/kg) was given as a slow intravenous bolus dose to induce anesthesia in patients without thoracic epidural anesthesia. All patients were ventilated with oxygen in air (FiO_2 = 0.4-0.5), supplemented with isoflurane or sevoflurane.

For cardiopulmonary bypass (CPB), a membrane oxygenator (Dideco Compactflo; Dideco S.p.A., Mirandola, Italy) fitted with a non-pulsatile pump flow by means of a Stöckert roller pump (CAPS or SIII; Stöckert GMBH, Munich, Germany) was used, with a systemic temperature drift down to 32-34°C. A 40 µm arterial line filter (D734; Dideco S.p.A.) was included in the CPB circuit. Although, between 1996 and 2002, conventional non-coated PVC tubing was used, since 2002 a phosphorylcholine-coated bypass circuit (Ph.I.S.I.O.; Dideco S.p.A.) has been used routinely by the present authors. Blood cardioplegia was utilized for cardiac protection in all cases. Cardiac arrest was initiated with a bolus dose of K/Mg-cardioplegia concentrate solution, administered via a warm (35-37°C) mixture of a moderately hyperkalemic 5% glucose solution and oxygenated blood infused into the aortic root, at a ratio of 1:8. The mixture was cooled to approximately 30°C after cardiac arrest, and administered thereafter as a continuous antegrade/retrograde infusion directly into the coronary ostia and/or through the coronary sinus, and into the venous grafts. Before declamping the aorta the blood cardioplegia was warmed to 35-37°C and infused for 4-5 min. The target activated clotting time was ≥600 s, due to the use of a moderate dose of aprotinin ($2.5\text{-}4\times10^6$ units per patient).

Table I: Preoperative[a] and operative data for patients who underwent aortic valve replacement with or without coronary artery bypass surgery.

Variable	Value
Age (years)	69 ± 11
Female gender (n)	186 (41)
Body mass index (kg/m²)	28±5
Percentage of predicted FEV_1	88 ± 17**
Percentage of predicted FVC	82 ± 18**
History of smoking (n)[b]	115 (23)
Current smoker (n)[b]	36 (8)
Pulmonary disease (n)[c]	61 (14)**
Diabetes (n)	70 (16)
Serum creatinine (mol/l)	90 ± 41
Cerebrovascular disease (n)	37 (8)*
Neurological dysfunction (n)	3 (1)
Myocardial infarction <3 months (n)	17 (4)
Extracardiac arteriopathy (n)	23 (5)
Previous vascular/endovascular surgery (n)	11 (2)
Previous cardiac surgery (n)	18 (4)
LVEF (%)	54 ± 11
Unstable angina pectoris (n)	6 (1)*
Critical preoperative status (n)	6 (1)
Active endocarditis (n)	7 (2)
PASP >60 mmHg (n)	14 (3)
Emergency operation (n)	3 (1)
Indication for surgery (n)	
Aortic valve stenosis	281 (62)
Aortic valve regurgitation	64 (14)
Combined aortic valve disease	98 (22)
Other	10 (2)
Additive EuroSCORE	6 ± 3**
Logistic EuroSCORE (%)	7 ± 8**
Coronary artery bypass surgery (n)	224 (49)
No. of distal anastomoses	2.8 ± 1.4
No. of proximal anastomoses	1.7 ± 0.9
Aortic cross-clamp time (min)	111 ± 37
Cardiopulmonary bypass time (min)	144 ± 51*

Continuous variables are reported as mean ± SD (unless otherwise indicated).
Values in parentheses are percentages.
[a]Definition criteria for preoperative variables are according to EuroSCORE.
[b]Data missing from 18 patients.
[c]Classified as use of bronchodilators or steroids for COPD/asthma.
*$p < 0.05$; **$p < 0.01$; p-values refer to univariate analysis for prediction of in-hospital mortality.
LVEF: Left ventricular ejection fraction; PASP: Pulmonary artery systolic pressure.

Surgical technique

Surgery was undertaken via a median sternotomy. All procedures were prosthetic valve implantations, with the valve type being selected in consensus with the patient. The normal 'dividing point' between

Table II: Postoperative outcome.

Clinical end-point	Value
In-hospital mortality (n)	13 (3)
30-day mortality (n)	12 (3)
Resternotomy (n)	48 (10)
Mediastinitis (n)	3 (1)
Stroke (n)	16 (4)
Stroke or TIA	20 (4)
Intra-aortic balloon pump (n)	7 (2)
Acute renal failure requiring dialysis (n)	2 (1)
Delirium (n)	47 (10)
Atrial fibrillation (n)	245 (54)
Extubation time (h)*	8 ± 17
Reintubation (n)	21 (5)
Pneumonia (n)	35 (8)
Intensive care unit stay (days)*	2 ± 3
Intensive care unit stay ≥5 days (n)	28 (6)

*Continuous variables are reported as mean ± SD.
Values in parentheses are percentages.
TIA: Transient ischemic attack.

employing a mechanical or a biological valve was a patient age of 70 years.

The clinical and operative data are summarized in Table I; variables were categorized according to the EuroSCORE criteria (5). The operative risk has been estimated according to the EuroSCORE scoring method criteria (5), while pulmonary disease was classified according to the use of bronchodilators or steroids for the treatment of COPD/asthma.

The in-hospital mortality was considered to be the main outcome measure; other outcome end-points are listed in Table II.

Statistical analysis

All statistical analyses were performed using SPSS statistical software (v. 14.0.1; SPSS Inc., Chicago, IL, USA). Continuous variables were reported as mean ± SD. Pearson's chi-square test, Fisher's exact test and the Mann-Whitney *U*-test were each used for the univariate analysis. A receiver operating characteristics (ROC) curve was used to estimate the predictive value of the continuous variables. Spearman's test was used to estimate the correlation of continuous variables. Logistic regression with backward selection was used for multivariate analysis. Variables with a p-value <0.05 at univariate analysis were included into the regression model. A p-value <0.05 was considered to be statistically significant.

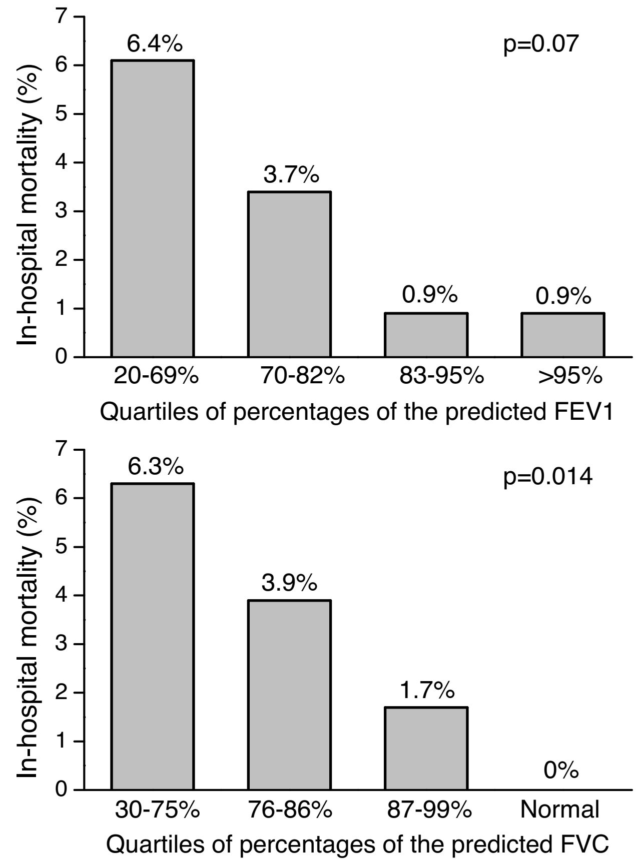

Figure 1: Observed in-hospital mortality rates according to quartiles of percentages of the predicted FVC and of the predicted FEV_1.

Results

Spirometry parameters

Patients undergoing AVR with CABG had similar spirometry parameters as those undergoing isolated AVR. The percentage predicted FVC (rho = 0.125, p = 0.009) and percentage predicted FEV_1 (rho = 0.113, p = 0.012) correlated with the preoperative left ventricular ejection fraction (LVEF). Similarly, these parameters were associated with EuroSCORE LVEF classes (p = 0.005 and p = 0.05, respectively). Interestingly, a LVEF <50% was significantly associated with the percentage predicted FVC <80% (30.6% versus 15.5%, p <0.0001), but not the percentage of predicted FEV_1 <75% (24.7% versus 18.1%, p = 0.11).

As expected, the percentages of predicted FEV_1, but not of predicted FVC (p = 0.11 and p = 0.097, respectively), were significantly lower among patients with history of smoking (74.7 ± 16.8% versus 84.3 ± 18.1%, p <0.0001) and current smokers (69.9 ± 13.6% versus 82.8 ± 18.3%, p <0.0001).
The percentages of predicted FVC and FEV_1 did not correlate with the CPB time.

Pulmonary disease and in-hospital mortality

The immediate outcome end-points are summarized in Table II. When all variables listed in Table I which had a p-value <0.05 at univariate analysis were included into the regression analysis, the percentages of predicted FVC (OR 0.952; 95% CI 0.914-0.990; p = 0.019), unstable angina pectoris (OR 12.981; 95% CI 1.618-104.126; p = 0.016) and CPB duration (OR 1.010; 95% CI 1.004-1.102; p = 0.001) were independent predictors of in-hospital mortality. These variables remained independent predictors even when the logistic EuroSCORE was included into the logistic regression analysis. The percentages of predicted FVC (AUC 0.749; 95% CI 0.632-0.866; p = 0.002) and of the predicted FEV_1 (AUC 0.723; 95% CI 0.591-0.854; p = 0.003) had satisfactory areas under the ROC curve. The best cut-off value for the percentage of predicted FVC was 80% (in-hospital mortality 6.3% versus 1.3%; p = 0.005; OR 5.100; 95% CI 1.544-16.849; specificity 69%, sensitivity 69%) and for the percentage of predicted FEV_1 was 75% (in-hospital mortality 5.2% versus 1.7%; p = 0.04; OR 3.233; 95% CI 1.039-10.056; specificity 67%, sensitivity 62%). A history of pulmonary disease was also associated with an increased risk of in-hospital mortality (9.7% versus 1.8%; OR 5.893; 95% CI 1.911-18.167; p = 0.004). However, even when the percentage of predicted FVC <80% and of predicted FEV_1 <75% were included into the regression analysis, only the percentage of predicted FVC was, again, an independent predictor of adverse outcome. The mortality rates of different quartiles of percentages of the predicted FVC and FEV_1 are shown in Figure 1.

Impact of pulmonary disease on the other outcome end-points

The percentage of predicted FVC was significantly associated with postoperative stroke (p = 0.008), but neither the percentage of predicted FEV_1 (p = 0.21) nor any history of pulmonary disease (p = 0.25) were associated with this complication. When adjusted for cerebrovascular disease, neurological dysfunction, redo-surgery, CPB time and aortic cross-clamp time (which were significantly associated with postoperative stroke at univariate analysis), only the percentage of predicted FVC was found to be an independent predictor of stroke (OR 0.956; 95% CI 0.923-0.989; p = 0.009). A percentage of the predicted FVC <80% was associated with a risk of postoperative stroke of 6.9% versus 1.9% among those patients with better FVC values (OR 3.769; 95% CI 1.342-10.581; p = 0.012). Stroke rates for decreasing quartiles of percentage of the predicted FVC were 1.6%, 1.7%. 3.9% and 7.1% (p=0.10), respectively. Similarly, the percentage of predicted FVC was significantly associated with stroke and/or transient ischemic attack (Mann-Whitney *U*-test: p = 0.008; for 80% cut-off value: 8.3% versus 2.6%, p = 0.006, OR 3.420, 95% CI 1.366-8.536, p = 0.006).

Interestingly, the percentages of predicted FVC and of predicted FEV_1, and a history of pulmonary disease, were not associated with postoperative pneumonia, which otherwise was significantly associated with extracardiac arteriopathy (p = 0.025), CPB time (p = 0.004) and aortic cross-clamp time (p <0.0001).

The percentages of predicted FVC (rho: -0.139, p = 0.003) and of predicted FEV_1 (rho: -0.093, p = 0.050) were negatively correlated with extubation time, although the correlation coefficients were rather small. Only the percentage of predicted FVC correlated with the length of stay in the intensive care unit (rho: -0.127, p = 0.007). The percentage of predicted FVC <80% (10.4% versus 4.2%, OR 2.648, 95% CI 1.225-5.724, p = 0.011) and a history of pulmonary disease (13.1% versus 5.1%, OR 2.808, 95% CI 1.117-6.694, p = 0.016) were significantly associated with a higher risk of intensive care unit stay of five or more days.

Discussion

Cardiac surgery, by its very nature, alters both pulmonary and cardiac mechanics (14). The effects related to median sternotomy, the use of CPB, depressed postoperative cardiac function, and manipulation of the thoracic contents, each contribute to postoperative derangements of pulmonary function. Pulmonary complications are believed to be mainly related to depressed postoperative cardiac function (14). In fact, a postoperative low cardiac output leads to cardiogenic pulmonary edema, as well as to severe muscle fatigue with secondary poor chest mobility, ineffective coughing and lack of deep breathing. These events are further complicated by the systemic inflammatory response related to surgery and the use of CPB (15), the lungs being the main target of this inflammatory response. Thus, it is not unexpected that patients with a poor preoperative pulmonary function would experience an adverse postoperative outcome.

The results of the present study suggest that preoperative pulmonary function testing could be of benefit in identifying high-risk patients. These findings are especially important in view of recent studies which have shown an improved outcome in patients undergoing pulmonary rehabilitation before CABG (16,17). However, the present study results did not show any association between preoperative poor lung function and pneumonia, but rather identified those patients who were at risk of dying from non-pulmonary complications. In this sense, the percentages of predicted FEV_1 and FVC that were evaluated had the merit to identify those patients who were in poor general condition, along with poor lung function. It is worth noting that this was independent of any smoking habits. It has been observed that spirometric parameters could be a surrogate of extrapulmonary conditions associated with postoperative stroke. In fact, current evidence suggests that COPD per se has systemic effects, which contribute to the poor prognosis of these patients (18). Several studies have established that COPD is associated with low-grade systemic inflammation, which is partly independent of smoking (19). Such a systemic inflammation is likely to be a major contributor in the pathogenesis of adverse effects of COPD, including weight loss, skeletal muscle dysfunction, cardiovascular disease, depression and osteoporosis (18). Importantly - and in contrast to most of the risk factors that contribute to adverse immediate and late outcomes of patients undergoing cardiac surgery - COPD is to some extent a treatable disease. Sin and Man (20) have shown that corticosteroids significantly reduced the plasma levels of C-reactive protein in these patients. Interestingly, a very low dose of inhaled steroids has been shown to reduce the risk of myocardial infarction in COPD patients (21). In the TORCH study, a combined treatment with salmeterol and fluticasone reduced the risk of death by 17.5% in patients with moderate and severe COPD (22). Furthermore, potential beneficial effects in terms of early and late survival with the use of angiotensin-converting enzyme inhibitors and statins have been reported in patients with COPD (23,24).

The question remains, therefore, as to whether the identification and treatment of this condition could improve the immediate postoperative outcome after AVR. The present study was not planned to answer this issue, and the results suggest only the prognostic importance of pulmonary disease in these patients. Deaths secondary to cardiovascular and pulmonary complications, as well as to multiorgan failure, are potentially preventable by improving pulmonary function, as well as the oxyhemodynamics. A short-term treatment with corticosteroids has been shown to improve pulmonary function and the immediate outcome of patients undergoing CABG (25,26). Other studies (16,17) have shown that preoperative pulmonary rehabilitation improves the outcome after CABG. Unfortunately, however, there is as yet insufficient evidence regarding the potential benefits of preoperative pulmonary rehabilitation/medical treatment before cardiac surgery. It is likely that patients with COPD undergoing cardiac surgery would, in any case, benefit from these therapeutic measures to the same extent as would non-surgical COPD patients (27).

The present findings suggest that that the percentage of predicted FVC has a somewhat better prognostic importance than the percentage of predicted FEV_1. Whilst this seems to contradict the findings in patients undergoing CABG (10,11), it is likely that hemodynamic changes associated with severe aortic valve disease may result in lung changes. This could contribute to a different pattern of pulmonary disease among patients undergoing isolated CABG compared to those undergoing AVR. Recently, chronic heart failure has been shown to be associated with restrictive lung changes (28). The present findings confirm that a low LVEF correlates more with values of FVC than with FEV_1.

In conclusion, the study results suggest that pulmonary disease, as indicated by decreased FVC and FEV_1, is an important comorbidity factor in patients undergoing AVR surgery. Further studies are required to demonstrate whether the identification and treatment of these patients could improve their outcome after AVR.

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Coronary Artery Bypass Surgery in Octogenarians: Long-Term Outcome Can Be Better Than Expected

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Background. We have reviewed our experience with octogenarians undergoing coronary artery bypass grafting.

Methods. A consecutive series of 274 patients age 80 years or greater out of 3,474 patients who underwent isolated coronary artery bypass grafting. We have assessed the intrinsic risk aged 80 years or greater by comparing them with a propensity score-matched cohort of younger patients with similar operative risk (other than age).

Results. Thirty-day mortality (4.7% vs 1.3%, $p < 0.0001$), combined adverse event rates (13.1% vs 6.6%, $p < 0.0001$), and five-year survival (76.6% vs 90.4%, $p < 0.0001$) were significantly poorer among patients aged 80 years or greater as compared with younger patients. These figures were, however, better than estimates of a recent systematic review by McKellar and colleagues (McKellar SH, Brown ML, Frye RL, Schaff HV, Sundt TM III. Comparison of coronary revascularization procedures in octogenarians: a systematic review and meta-analysis. Nat Clin Pract Cardiovasc Med 2008;5:738–46) (30-day mortality 7.2%, and five-year survival, 68%). When octogenarians were compared with 273 propensity score-matched patients aged less than 80 years, the 30-day mortality (4.8% vs 2.6%, $p = 0.17$) and combined adverse event rates (13.2% vs 10.6%, $p = 0.36$) did not significantly differ. Five-year survival, despite statistical significance, was not remarkably lower than that of propensity-matched patients aged less than 80 years (77.0% vs 81.3%, $p = 0.009$). The decrease in survival of octogenarians was evident only during the first few months after surgery, but not later on.

Conclusions. The results of this study suggest that immediate and five-year survival of octogenarians undergoing coronary artery bypass grafting may be even better than previously estimated. Survival of octogenarians may be suboptimal only during the first few months after surgery, whereas at five years may not differ remarkably from younger patients with otherwise similar operative risk.

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In Finland, from 1980 to 2008 the prevalence of persons aged 80 years or greater has increased from 1.8% to 4.5% [1]. This introduces an increase in the burden of health care for this continuously growing greying population. In particular, revascularization procedures for coronary artery disease are becoming more common. In the United States, the prevalence of coronary revascularization among patients aged 75 to 84 years increased from 69.1 per 10,000 population in 1990 to 140.0 per 10,000 population in 2006, and in patients aged 85 years or greater increased during the same period from 14.0 to 59.9 per 10, 000 population [2]. This, in part, is due to a more confident approach toward coronary revascularization in this high-risk patient population.

McKellar and colleagues [3] have exhaustively summarized the rather good immediate and five-year outcome of octogenarians after coronary artery bypass surgery (CABG) and percutaneous coronary intervention (PCI). Although the latter can intuitively be associated with lower immediate postoperative mortality rates (estimates according to McKellar and colleagues: PCI 5.4% vs CABG 7.2%), CABG is very often the only feasible treatment for these patients who have diffuse coronary artery disease. Indeed, cardiac surgeons not infrequently are called upon to care for octogenarians with unstable angina pectoris and (or) acute heart failure unresponsive to medical treatment and (or) PCI. The latter introduce a bias which prevents any comparative analysis between CABG and PCI in octogenarians.

Age is a remarkably important risk factor in cardiac surgery, but it is not easy to discern the impact of age from the comorbidities accompanying the elderly. Herein, we have reviewed our experience with octogenarians undergoing CABG and we attempted to assess the intrinsic risk of age 80 years or greater by comparing the latter patients with a propensity score-matched co-

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Table 1. Clinical and Operative Data of Patients Aged 80 Years or Greater and Less Than 80 Years, and Who Underwent Isolated Coronary Artery Bypass Surgery

	Overall Series			Propensity Score-Matched Pairs		
Variable	Octogenarian Patients (n = 274) (%)	Younger Patients (n = 3,200) (%)	*p* Value	Octogenarian Patients (n = 273) (%)	Younger Patients (n = 273) (%)	*p* Value
Age (years)	82.5 ± 1.9	66.6 ± 8.8	<0.0001	82.5 ± 1.9	70.5 ± 6.8	<0.0001
Females	110 (40.1)	761 (23.8)	<0.0001	109 (39.9)	109 (39.9)	1.00
Pulmonary disease	24 (8.8)	356 (11.1)	0.23	24 (8.8)	37 (13.6)	0.08
Diabetes	63 (23.0)	618 (19.3)	0.14	63 (23.1)	69 (25.3)	0.55
Renal failure	3 (1.1)	28 (0.9)	0.73	3 (1.1)	4 (1.5)	0.73
Cerebrovascular disease	42 (15.3)	373 (11.7)	0.07	41 (15.0)	43 (15.8)	0.81
Neurologic dysfunction	5 (1.8)	34 (1.1)	0.25	5 (1.8)	3 (1.1)	0.73
Myocardial infarction<3 months	106 (38.7)	628 (19.6)	<0.0001	105 (38.5)	105 (38.5)	1.00
Extracardiac arteriopathy	30 (10.9)	270 (8.4)	0.16	30 (11.0)	26 (9.5)	0.57
Previous cardiac surgery	0 (0)	126 (3.9)	<0.0001	0 (0)	17 (6.2)	<0.0001
LVEF ≤ 0.50	89 (0.325)	10 (0.342)	0.56	89 (0.326)	98 (0.359)	0.42
Unstable angina pectoris	53 (19.3)	417 (13.0)	0.003	53 (19.4)	58 (21.2)	0.60
Critical preoperative status	6 (2.2)	33 (1.0)	0.08	6 (2.2)	11 (4.0)	0.22
Systolic pulmonary a. pressure >60 mm Hg	2 (0.7)	18 (0.6)	0.67	2 (0.7)	3 (1.1)	0.69
Emergency operation	21 (7.7)	180 (5.6)	0.17	21 (7.7)	29 (10.6)	0.24
Additive EuroSCORE	7.6 ± 2.4	3.9 ± 2.7	<0.0001	7.6 ± 2.4	5.6 ± 3.0	<0.0001
Logistic EuroSCORE (%)	10.6 ± 9.3	4.3 ± 5.6	<0.0001	10.6 ± 9.6	7.0 ± 8.2	<0.0001
Higgins score	3.8 ± 2.2	2.4 ± 2.4	<0.0001	3.8 ± 2.2	3.5 ± 2.8	0.002
At least one mammary artery graft	220 (80.3)	2986 (93.3)	<0.0001	219 (80.2)	219 (80.2)	1.00
Bilateral mammary artery graft	3 (1.1)	515 (16.1)	<0.0001	2 (0.2)	2 (0.2)	1.00
No. of distal anastomosis	4.1 ± 1.1	4.1 ± 1.3	0.61	4.1 ± 1.1	3.9 ± 1.2	0.13
Beating heart surgery	54 (19.7)	288 (9.0)	<0.0001	53 (19.4)	53 (19.4)	1.00
Aortic cross-clamping time (minutes)	71 ± 30	80 ± 28	<0.0001	71 ± 30	73 ± 31	0.50
Cardiopulmonary bypass time (minutes)	101 ± 24	103 ± 31	0.44	101 ± 24	105 ± 34	0.45

Definition criteria for preoperative variables are according to EuroSCORE.

Continuous variables are reported as mean ± standard deviation.

Values in parentheses are percentages.

EuroSCORE = European system for cardiac operative risk evaluation; LVEF = left ventricular ejection fraction.

hort of younger patients with similar operative risk (other than age).

Material and Methods

This study included a consecutive series of 274 patients aged 80 years or greater (only one patient was 90-years old) who underwent isolated CABG from 1994 to 2008 at Vaasa Central Hospital, Vaasa, Finland. The study protocol was approved by the Ethics Committee of Vaasa Central Hospital and a waiver of the requirement of written informed consent was obtained.

These patients belong to a series of 3,474 patients who underwent isolated CABG during the study period. All of them had complete data regarding the European system for cardiac operative risk evaluation (EuroSCORE) variables [4]. No attempt to replace missing values has been done. Clinical variables have been classified according to EuroSCORE criteria. Data on these patients were entered prospectively into an institutional database and are summarized in Table 1. The operative risk was assessed by EuroSCORE and Higgins score [5].

The anesthesia method consisted of combined general anesthesia. Thoracic epidural anesthesia was used at the discretion of the anesthesiologist for patients with anticipated pulmonary or other significant risk. When conventional CABG was carried out, a blood cardioplegia technique was employed for cardiac protection and it was given as a continuous anterograde-retrograde infusion.

Epiaortic ultrasound was performed in most of these patients. The decision to avoid aortic cross- or side-clamping was based on intraoperative findings of diseased ascending aorta and individual operative risk.

Heartstring anastomosis seal device (Guidant Corporation, San Jose, CA) was used whenever severely calcified ascending aorta prevented its safe cross-clamping and side-clamping. Data on late death were retrieved from the National Registry of Statistics Finland (Tilastokeskus).

Statistical Analysis

Statistical analysis was performed using SPSS statistical software (SPSS v. 16.0.1; SPSS Inc, Chicago, IL). Continuous variables are reported as the mean ± standard deviation. The Pearson test, the Fisher exact test (with or without the Monte Carlo method), the Mann-Whitney test, and the Kruskall-Wallis test were used for univariate analysis. Because patients aged 80 years or greater had an operative risk markedly higher (as indicated by EuroSCORE and Higgins score) than younger patients, which can be partly explained by the age, we have calculated a propensity score to get one-to-one match pairs with similar clinical and operative characteristics (other than age). Indeed, elderly patients also have been operated on employing, less frequently, one or two bilateral mammary artery grafts. Logistic regression with backward selection was performed to calculate the propensity score. All variables but age, EuroSCORE, and Higgins score (listed in Table 1) with a p less than 0.20 have been included into the regression model. Receiver operating characteristic curve analysis was used to estimate the area under the curve of the calculated propensity score. The latter was employed for one-to-one matching according to a difference in the propensity score less than 0.005. Long-term outcome has been assessed by the Kaplan-Meier test and Cox regression analysis. Only variables with a p less than 0.20 have been included into the regression model for prediction of immediate and late mortality. A p value of less than 0.05 was considered statistically significant.

Results

The prevalence of octogenarians has significantly increased over the years ($p < 0.0001$; Fig 1), reaching a rate of about 15% during the last years of our experience. The increasing prevalence of octogenarians was anyway associated also with a trend for increased 30-day mortality (1994 to 1998: 0%, 0 of 23 patients; 1999 to 2003: 4.5%, 4 of 88 patients; 2004 to 2008: 5.5%, 9 of 163, $p = 0.75$). However, this was likely due to a certain increase in the operative risk observed during the last decade (mean logistic EuroSCORE: 8.0%, 10.8%, and 10.9%, respectively, Kruskall-Wallis' test: $p = 0.48$) as well as a more confident and aggressive revascularization policy in this patient population.

Table 2 summarizes the postoperative complications as well as the immediate and long-term outcome. Octogenarians have a significantly poorer immediate and long-term outcome compared with younger patients. However, when compared with pooled survival estimates according to the study by McKellar and colleagues [3], the overall survival of octogenarians of the present series

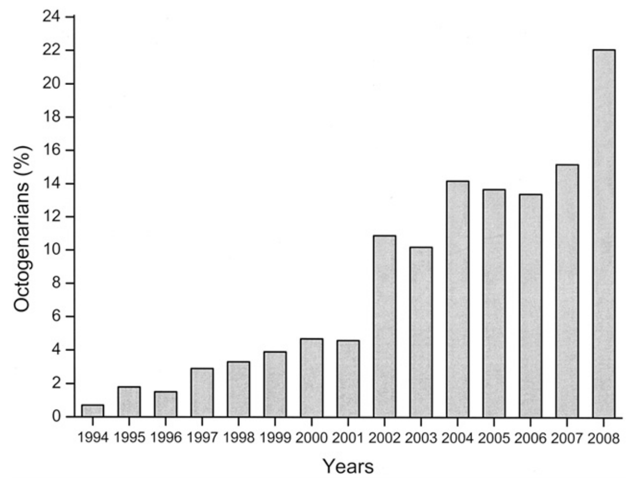

Fig 1. Increasing prevalence along the study period of patients aged 80 years or greater who underwent isolated coronary artery bypass surgery at Vaasa Central Hospital, Finland (Fisher exact test, Monte Carlo method: $p < 0.0001$).

is much better than the estimated one (Fig 2). This comparison could be affected by the inclusion into this systematic review of patients operated in the eighties.

Predictors of Immediate and Late Mortality Among Octogenarians

Univariate analysis showed that diabetes (9.5% vs 3.3%, $p = 0.04$) and critical preoperative status (50.0% vs 3.7%, $p = 0.002$) were the only preoperative variables predicting 30-day postoperative mortality. Logistic regression analysis showed that only critical preoperative status was independently associated with 30-day postoperative mortality ($p < 0.0001$, odds ratio 26.03, 95% confidence interval (CI) 4.38 to 154.65).

Univariate analysis showed that diabetes ($p < 0.0001$), extracardiac arteriopathy ($p = 0.006$), neurologic dysfunction ($p = 0.005$), renal failure ($p = 0.02$), critical preoperative status ($p < 0.0001$), unstable angina pectoris ($p = 0.004$), and recent myocardial infarction ($p = 0.001$) were associated with poorer long-term outcome. Cox regression analysis showed that recent myocardial infarction ($p = 0.04$, risk ratio (RR) 1.70, 95% CI 1.04 to 2.79), extracardiac arteriopathy ($p = 0.001$, RR 2.78, 95% CI 1.50 to 5.15), neurologic dysfunction ($p = 0.03$, RR 3.83, 95% CI 1.15 to 12.68), diabetes ($p < 0.0001$, RR 2.63, 95% CI 1.61 to 4.30), and critical preoperative status ($p < 0.0001$, RR 11.78, 95% CI 4.30 to 32.21) were independent predictors of late mortality.

Propensity Score Analysis

Propensity score analysis provided a model with a Hosmer-Lemeshow $p = 0.32$ and showed that the prevalence of female gender, recent myocardial infarction, at least one internal mammary artery graft used, bilateral mammary artery grafting, and beating heart surgery significantly differed between patients aged 80 years or greater and younger patients. The obtained propensity score had an area under the receiver operating characteristic curve of

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Table 2. Immediate Outcome After Isolated Coronary Artery Bypass Surgery in Octogenarians and Younger Patients

	Overall Series			Propensity Score-Matched Pairs		
Variable	Octogenarian Patients (n = 274) (%)	Younger Patients (n = 3,200) (%)	*p* Value	Octogenarian Patients (n = 273) (%)	Younger Patients (n = 273) (%)	*p* Value
Immediate postoperative outcome:						
30-day mortality	13 (4.7)	40 (1.3)	<0.0001	13 (4.8)	7 (2.6)	0.17
Reoperation	18 (6.6)	161 (5.0)	0.27	18 (6.6)	20 (7.3)	0.74
Reoperation for bleeding	9 (3.3)	106 (3.3)	0.99	9 (3.3)	16 (5.9)	0.22
Stroke	7 (2.4)	7 (2.6)	0.88	7 (2.6)	6 (2.2)	0.78
Intraaortic balloon pump	6 (2.2)	26 (0.8)	0.02	6 (2.2)	5 (1.8)	0.76
Acute renal failure requiring dialysis	7 (2.6)	28 (0.9)	0.008	7 (2.6)	3 (1.1)	0.34
ICU stay (days)	2.0 ± 2.7	1.6 ± 3.5	<0.0001	2.0 ± 2.7	1.9 ± 3.2	0.21
ICU stay ≥ 5 days	24 (8.8)	121 (3.8)	<0.0001	24 (8.8)	19 (7.0)	0.43
Delirium	52 (19.0)	254 (8.0)	<0.0001	52 (19.1)	30 (11.1)	0.009
Pneumonia	21 (7.7)	177 (5.5)	0.14	21 (7.7)	18 (6.6)	0.62
Atrial fibrillation	143 (55.4)	1142 (36.5)	<0.0001	142 (55.3)	113 (43.6)	0.008
Combined adverse endpoint[a]	36 (13.1)	211 (6.6)	<0.0001	36 (13.2)	29 (10.6)	0.36
Late postoperative outcome:			<0.0001			0.009
1-year overall survival	90.8%	97.3%		90.8%	96.7%	
3-year overall survival	86.3%	93.9%		86.7%	90.5%	
5-year overall survival	76.6%	90.4%		77.0%	81.3%	
10-year overall survival	34.9%	76.1%		35.0%	55.3%	

[a] In-hospital mortality, stroke, length of stay in ICU ≥ 5 days, acute renal failure requiring dialysis.

Values in parentheses are percentages.

Late survival has been estimated by the Kaplan-Meier method with the log-rank test.

ICU = intensive care unit.

0.71 (95% CI 0.69 to 0.75, $p < 0.0001$). This propensity score provided 273 matched pairs with similar risk factors other than age (Table 1).

The immediate outcome of propensity score-matched pairs is summarized in Table 2. These findings demonstrate that, despite the evident negative prognostic impact of increased age, the immediate outcome of octogenarians does not significantly differ from that of younger patients with otherwise similar baseline risk factors and operated on with the same technical approach (ie, beating heart surgery and use of internal mammary artery grafts). Figure 3 shows the five-year overall survival which, despite the statistical significance, is not remarkably lower than that of propensity-matched patients aged less than 80 years (77.0% vs 81.3%, $p = 0.009$). The decrease in survival of octogenarians seems to be evident during the first few months after surgery, but not later on (Fig 3). Ten-year survival was, by the finite nature of life, rather poor (Table 2). Propensity score analysis, despite a rather good matching of patients, has not eliminated those patients who had prior cardiac surgery. When the latter were excluded, five-year overall survival rates were 77.0% among octogenarians versus 80.5% among patients aged less than 80 years ($p = 0.019$).

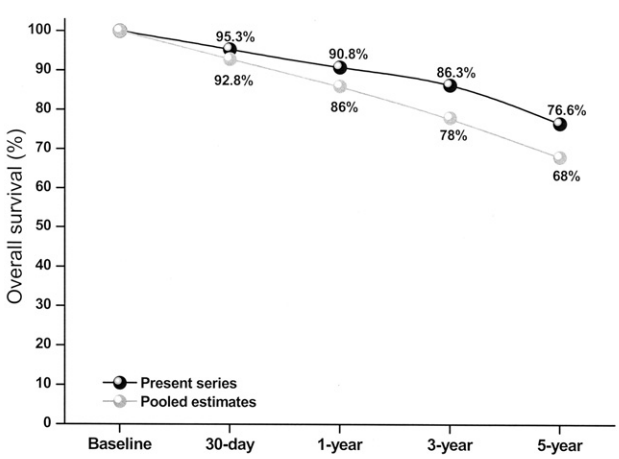

Fig 2. Overall survival rates of patients aged 80 years or greater who underwent isolated coronary artery bypass surgery in the present series (black circles) and according to pooled estimates (grey circles) reported by McKellar and colleagues [3].

Comment

A number of octogenarians are not referred to cardiac surgery because of lack of evidence-based criteria for referral, an age-related fading interest on neutralizing "premature death," skepticism among physicians and surgeons about any expected gain in quality of life in the presence of rather high operative risk, cost considerations,

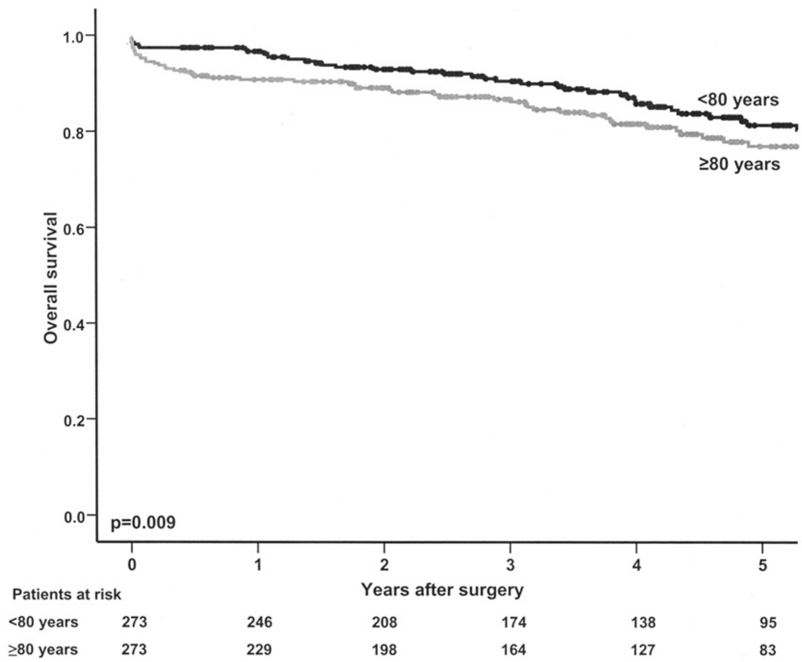

Fig 3. Overall survival rates of 273 propensity score-matched pairs of patients aged 80 years or greater and less than 80 years who underwent isolated coronary artery bypass surgery (log-rank: $p = 0.009$).

and finally, the patients themselves facing a difficult decision with limited, if any, emotional support from their relatives [6]. This introduces a remarkable bias in estimating the real risk and benefits associated with CABG as many patients are denied (or deny) a myocardial revascularization procedure. With these limitations in mind, the present study confirmed that the overall survival of these patients can be even better than that estimated by a recent systematic review [3] (Fig 2). This comparison could be affected by the inclusion into this systematic review of patients operated in the eighties, even if at that time a more conservative approach in treating octogenarians is likely to have been adopted. However, univariate analysis showed that more recent enrollment was associated with improved 30-day and one-year survival, but it did not affect long-term survival [3].

Furthermore, of particular importance is the gain in quality of life which octogenarians experience after cardiac surgery when compared with the age-adjusted and gender-adjusted general population [7–9], particularly when arterial grafts are used in these older patients. Women seem to receive the most benefit from cardiac operations in terms of quality of life [7]. However, even men, who are expecting to gain a quality of life similar to the age-adjusted and gender-adjusted general population, seem to receive an important benefit from CABG.

We have herein observed that CABG can be performed with results markedly better than expected. This encouraged us toward an even more aggressive policy over the years. However, we believe that the most important finding in this study is the fact that the risk of immediate postoperative complications was similar to that of a propensity-matched cohort of patients aged less than 80 years. This means that surgeons and cardiologists should decide to operate more on the basis of relevant risk factors rather than age itself. The most evident proof of this are the similar rates of combined adverse events that occurred in the propensity-matched pairs (octogenarians: 13.2% versus younger patients: 10.6%, $p = 0.36$). Furthermore, Figure 3 shows that the survival curve of octogenarians differed from that of the propensity score-matched group only during the first few months after surgery and later on was similar to the latter group. This suggests that it may be of paramount importance to improve the early outcome of these elderly patients as they are expected to experience a significant benefit in terms of five-year survival. Indeed, there is still room also for improving late survival; for example, by complete revascularization [10] using arterial grafts [9], and a policy of aggressive secondary prevention [11].

Worth noting is the rather low rate of postoperative stroke herein observed. This is a major finding of this study which likely is the result of our policy of intraoperative screening for diseased ascending aorta along with avoidance of aortic manipulation when indicated.

Although retrospective in nature, this study shows that CABG is a highly effective treatment also in octogenarians with acceptable short-term risks and excellent five-year survival rates. Ten-year survival rate is not brilliant and simply reflects the finite nature of our lives. Together with findings of other studies demonstrating improved quality of life after CABG in octogenarians, it is important to make such results public among patients and referrers. The message to them is clear; age alone cannot be accepted as a sufficient criterion for not considering CABG surgery seriously as a treatment option.

In conclusion, the results of this study suggest that immediate and five-year survival of octogenarians undergoing CABG can be even better that previously estimated. Survival of octogenarians may be lower only during the first few months after surgery, whereas at five years may not differ remarkably from younger patients with otherwise similar operative risk.

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INVITED COMMENTARY

The more we read or write regarding surgical outcomes in octogenarians, the greater we miss specific measurements that might better describe the accumulation of somatic and functional damage associated with aging. Would it not be useful that whatever information is currently vehicled by "age" itself or summarized by a "fit for surgery" dummy variable could be broken down into a number of socioeconomic, physical, and mental functioning factors? Is there any other alternative to improve the accuracy of risk profiling of the elderly, along with our understanding of similarities and differences among different studies?

It is the lack of this kind of information that makes it difficult to put into perspective the outstanding 77% 5-year survival rate, as achieved by Nissinen and colleagues [1] in their octogenarians who underwent coronary artery bypass grafting. In order to do so, the authors [1] used for reference a series with an inadequately characterized risk profile pooled from different units, different geographic sources, and different eras. They also warned us that such an unadjusted comparison cannot be overly relied upon. On the other hand, balancing scores are not ideally suited for resuscitating similarities already buried, did they ever exist, by a strict selection process upstream. Nor do balancing scores adjust, by definition, for the unmeasured and unmeasurable confounding so prevalent when selecting very old patients for surgery.

In addition, a landmark analysis would have shown the survival curves of Nissinen and colleagues' [1] matched groups to be superimposed from month 6 through the 5-year term. Unfortunately, the authors did not provide background information from life tables of an age- and sex-matched normal population, which likely would have shown quite separate and diverging survival curves due to age differences between groups. Therefore, it is not known whether in this study [1] octogenarians fared better or if the control group fared worse than expected, although both of these conclusions may be true.

Finally, the authors state that the low rate of immediate postoperative complications was the most important finding in this study, and I definitely concur with this conclusion because the complications may independently affect both early and late survival. In fact, we have found that early complications may be independent predictors of death in the late hazard phase, although whether this is a consequence of an ongoing "toxic," macro-apoptotic effect or rather expresses a propensity for both early and late adverse events remains to be seen.

Although excellent surgery is a key factor to success, as in Nissinen and colleagues' [1] series, we should appreciate that heterogeneity increases with advancing age and that further progress will require us to better understand that and fully account for it.

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Safe time limits of aortic cross-clamping and cardiopulmonary bypass in adult cardiac surgery

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Abstract

Objectives: We evaluated the impact of aortic cross-clamping time (XCT) and cardiopulmonary bypass time (CPBT) on the immediate and late outcome after adult cardiac surgery and attempted to identify their safe time limits.
Methods: This study includes 3280 patients who underwent adult cardiac surgery of various complexities. Myocardial protection was achieved with tepid continuous antegrade/retrograde blood cardioplegia.
Results: Receiver operating characteristics (ROC) curve analysis showed that XCT (area under the curve, AUC: 0.66), CPBT (AUC: 0.73) and CPBT with unclamped aorta (AUC: 0.77) were significantly associated with 30-day postoperative mortality. XCT of increasing 30-minute intervals (Odds Ratio (OR) 1.21, 95%C.I. 1.01-1.52) and CPBT of increasing 30-minute intervals (OR 1.47, 95%C.I. 1.27-1.71) were independent predictors of 30-day mortality. The best cutoff value for XCT was 150 min (30-day death: 1.8% vs. 12.2%, adjusted OR 3.07, 95%C.I. 1.48-6.39, accuracy 91.5%) and for CPBT 240 min (30-day death: 1.9% vs. 31.5%, adjusted OR 8.78, 95%C.I. 4.64-16.61, accuracy 96.0%). These parameters were significantly associated also with postoperative morbidity, particularly with postoperative stroke.
Conclusions: XCT and CPBT are predictors of immediate postoperative morbidity and mortality. In our experience, cardiac procedures with CPBT<240 min and XCT<150 min were associated with a rather low risk of immediate postoperative adverse events independently of the complexity of surgery patient's operative risk.

Keywords
cardiopulmonary bypass; aortic cross-clamping; perfusion; duration; safe limit

Introduction

During the last decades, many methods have been developed to provide optimal myocardial and non-cardiac organ protection during cardiac surgery. Myocardial protection can be achieved in different ways and recent systematic reviews seem to favour blood cardioplegia.[1,2] Whether cardioplegia should be administered in an antegrade or an antegrade/retrograde way and the optimal cardioplegia temperature are still matters of debate. The recent introduction of new perfusion systems is thought also to improve the safety of cardiopulmonary bypass and non-cardiac organ protection, but, so far, evidence of such benefits is still lacking.[3] In view of the limits of current methods, minimizing aortic cross-clamping time (XCT) and cardiopulmonary bypass time (CPBT) is certainly one of the most important issues in cardiac surgery. Indeed, CPBT has been shown to be associated with enhanced inflammatory response[4,5] and increased morbidity and mortality after pediatric and adult cardiac surgery.[6,7] In this study, we evaluated the impact of XCT and CPBT on the immediate outcome after adult cardiac surgery and attempted to identify their safe time limits.

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Material and methods

This study includes a series of 3280 patients who underwent adult cardiac surgery at Vaasa Central Hospital, Vaasa, Finland, from January 1994 to June 2008. Data on these patients were collected prospectively into an institutional cardiac surgery database. Only the first procedure for each patient was entered into the registry. Any other operation performed during the same in-hospital stay was not coded as a further procedure, but rather as a complication.

These patients belong to a series of 4563 patients who underwent cardiac surgery during the study period. Patients who underwent a cardiac procedure with the beating heart technique and those without data on preoperative serum creatinine and left ventricular ejection fraction were excluded from this analysis. Patients who underwent isolated minor procedures, such as pericardiectomy or for arrhythmias, have been excluded as well. No attempt to replace missing values has been done.

Data on late death were retrieved from the National Registry of Statistics Finland (Tilastokeskus).

Risk factor and definition criteria

Variables have been classified according to EuroSCORE criteria[8] and additive and logistic EuroSCOREs were calculated according to the proposed formulas.[8,9] Preoperative glomerular filtration rate was estimated according to the modified Modification of Diet in Renal Disease study equation.[10]

In order to estimate the impact of complex surgery on the immediate and late outcome, we have categorized major cardiac procedures as isolated, double or a combination of three to four procedures. This may reflect a longer XCT and CPBT and, probably, more technically demanding procedures. Herein, we refer to isolated or multiple procedures according to the number of procedures on each major anatomical structure (coronary arteries, heart valves, ascending aorta/aortic arch, atrial or ventricular septum). Surgery for cardiac tumors was considered as a major cardiac procedure.

Anesthesia and cardiopulmonary bypass

The anesthesia method consisted of combined general anesthesia. Thoracic epidural anesthesia was used at the discretion of the anesthesiologist for patients with anticipated pulmonary or other significant risk. Fentanyl 3-3.5ug/kg and propofol 0.8-2mg/kg were given intravenously for anesthesia induction, followed by continuous infusion of propofol 1-2mg/kg/h. Pancuronium 0.10mg/kg was given for muscle relaxation. Clonidine 1.5-2ug/kg was given as a slow intravenous bolus dose at induction of anesthesia to patients without thoracic epidural anesthesia. Patients were ventilated with oxygen in air, FiO_2 0.4-0.5, supplemented with isoflurane or sevoflurane.

For CPB, we used a membrane oxygenator (Dideco Compactflo; Dideco S.p.A., Mirandola, Italy) with a non-pulsatile pump flow by means of a Stöckert roller pump (CAPS or SIII, Stöckert GmbH, Munich, Germany) or, from 2005 on, a centrifugal pump (Stöckert SCP, Sorin Group Deutschland GmbH, Munich, Germany). Generally, we have used a systemic temperature drift down to 32-34°C. A 40μm arterial line filter (D734, Dideco S.p.A.) was included in the CPB circuit. From 1994 to 2002, we used conventional non-coated PVC-tubing, but, from 2002, we have routinely used a phosphorylcholine-coated bypass circuit (Ph.I.S.I.O., Dideco S.p.A.) and, from 2005 on, we have used a modified ECC.O mini-bypass circuit (Dideco S.p.A.) in part of the cases. A blood cardioplegia technique was employed for cardiac protection in all cases. Cardiac arrest was initiated with a bolus dose of K/Mg-cardioplegia concentrate solution given into a 35 to 37°C warm mixture of a moderately hyperkalemic 5% glucose solution and oxygenated blood infused into the aortic root in a ratio of 1:8. The mixture was cooled to 28-30°C after cardiac arrest and thereafter given as a continuous ante/retrograde infusion directly into the coronary ostia and/or through the coronary sinus and into the venous grafts. Before declamping of the aorta, the blood cardioplegia was warmed to 35 to 37°C and infused for 4 to 5 minutes. The target activated clotting time was ≥ 600 sec due to use of a moderate dose of aprotinin (2.5-4 million units).

Graft anastomoses to the ascending aorta were carried out with a single cross-clamp technique.

Outcome measures

The main outcome end-point of this study is 30-day postoperative mortality. The other outcome end-points are severe complications, such as intensive care unit stay ≥ 5 days, stroke, postoperative use of intra-aortic balloon pump (IABP), and de novo postoperative dialysis, and combined severe complications (any of 30-day postoperative death, intensive care unit stay ≥ 5 days, stroke, postoperative use of IABP, and de novo postoperative dialysis).

Statistical analysis

Statistical analysis was performed using SPSS statistical software (SPSS v. 14.0.1, SPSS Inc., Chicago, IL., USA). Continuous variables are reported as the mean ± standard deviation. The Pearson's Chi-square test, Fisher's exact test, the Kruskal-Wallis test and the Mann-Whitney test were used for univariate analysis. Correlation between continuous variables was estimated by the Spearman test. Receiver operating characteristics (ROC) curve was used to estimate the predictive value of continuous variables.

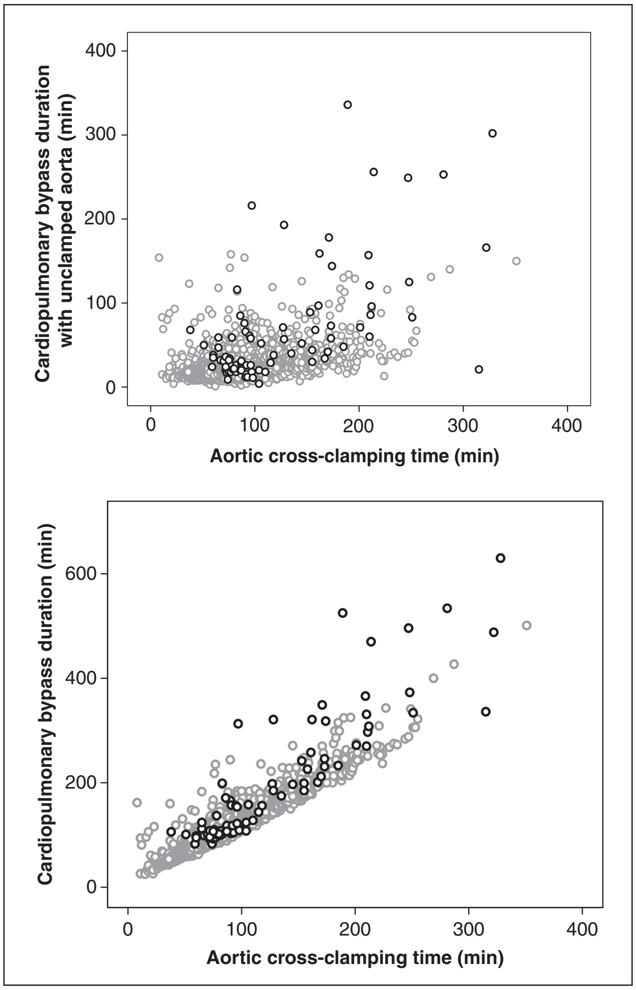

Figure 1. Aortic cross-clamping time strongly correlated with cardiopulmonary bypass duration (rho: 0.941, p<0.0001). The correlation between aortic cross-clamping time and cardiopulmonary bypass time with unclamped aorta was somewhat weaker (rho: 0.439, p<0.0001). Black circles indicate patients who died during 30-day postoperative period.

The best cutoff values have been chosen according to the best sensitivity, specificity, accuracy and adjusted Odds Ratio. Logistic regression with the help of backward selection was used for multivariate analysis by including all the variables with a p<0.05 at univariate analysis. A p<0.05 was considered statistically significant.

Results

Aortic cross-clamping and cardiopulmonary bypass time

Cross-clamp time, as expected, strongly correlated with CPBT (rho: 0.94, p<0.0001). However, the correlation between XCT and CPBT with an unclamped aorta was somewhat weaker (rho: 0.44, p<0.0001). Figure 1 shows a scattered correlation, indicating that a prolonged XCT was not necessarily associated with prolonged CPBT with unclamped aorta.

30-day postoperative mortality

Thirty-day postoperative mortality rate was 2.5% (83/3280). Additive EuroSCORE (p<0.0001, AUC 0.837, 95%C.I. 0.791-0.882) and logistic EuroSCORE (p<0.0001, AUC 0.84, 95%C.I. 0.80-0.89) performed well in predicting 30-day postoperative mortality.

Thirty-day mortality rate was not significantly different after isolated coronary artery bypass surgery (1.6%), isolated aortic valve surgery (1.7%) and isolated mitral valve surgery (1.7%) (p=0.75). On the other hand, 30-day mortality rates after isolated procedure, double procedure and three-to-four procedures were 1.7% (47/2820), 5.4% (22/404) and 25% (14/56), respectively (p<0.0001). Accordingly, the XCTs of (83±26 min, 134±36 min and 191±56 min, respectively, p<0.0001) and the CPBT of (106±34 min, 173±52 min and 262±98 min, respectively, p<0.0001) correlated with the complexity of the operation.

ROC curve analysis showed that XCT (p<0.0001, AUC: 0.66, 95%C.I. 0.60-0.73), CPBT (p<0.0001, AUC: 0.73, 95%C.I. 0.67-0.78), and CPBT with unclamped aorta (p<0.0001, AUC: 0.77, 95%C.I. 0.71-0.83) were associated with 30-day postoperative mortality. The increasing risk of 30-day mortality along with increased XCT and CPBT is depicted in Figure 2.

The results of logistic regression for predicting 30-day mortality are summarized in Tables 1 and 2 (Hosmer-Lemeshow's test: p=0.244). This regression model showed that both XCT and CPBT were independent predictors of immediate postoperative death. It is worth noting that, in the correlation matrix, XCT and CPBT were negatively correlated. Thus, XCT and CPBT were included into the regression model separately and the results where similar. XCT of increasing 30-minute intervals (p=0.04, OR 1.24, 95%C.I. 1.01-1.52, Hosmer-Lemeshow's test: p=0.43, change in -2 Log likelihood: 4.45) and CPBT of increasing 30-minute intervals (p<0.0001, OR 1.47, 95%C.I. 1.270-1.71, Hosmer-Lemeshow's test: p=0.49, change in -2 Log likelihood: 24.28) were also independent predictors of 30-day postoperative mortality when included separately into the regression model.

The best cutoff value for XCT was 150 min (1.8% vs. 12.2%, p<0.0001, OR 3.07, 95%C.I. 1.48 -6.39 as adjusted for additive EuroSCORE and complexity of the operation; sensitivity 33.7%, specificity 93%, accuracy 91.5%) and for CPBT was 240 min (1.9% vs. 31.5%, p<0.0001, OR 8.78, 95%C.I. 4.64-16.61 as adjusted for additive EuroSCORE and complexity of the operation; sensitivity 27.8%, specificity 97.8%, accuracy 96.0%).

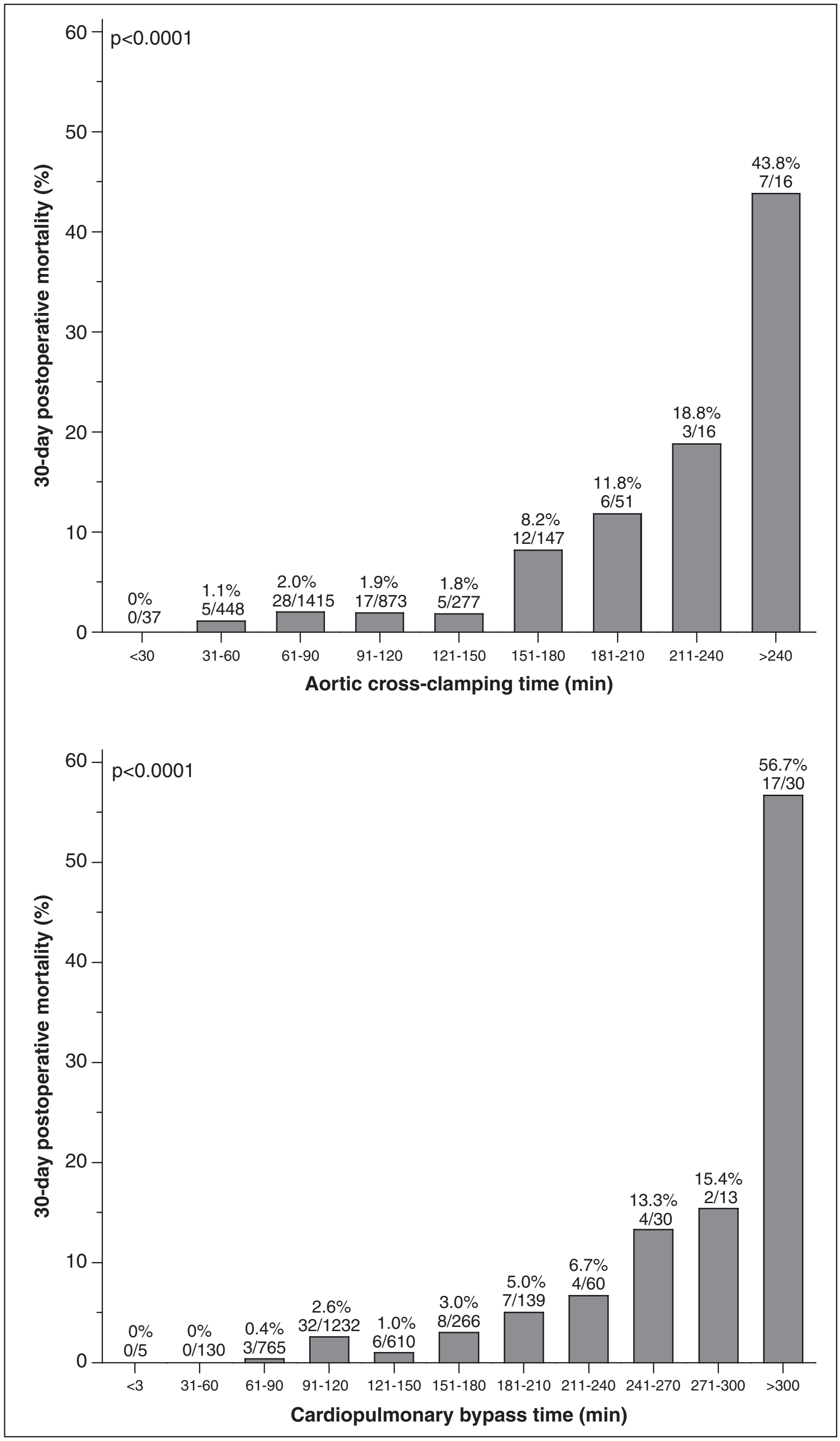

Figure 2. 30-day mortality rates for increasing duration of aortic cross-clamping ($p<0.0001$, O.R. 1.41, 95%C.I. 1.23-1.62 adjusted for additive EuroSCORE) and cardiopulmonary bypass ($p<0.0001$, O.R. 1.45, 95%C.I. 1.30-1.61 adjusted for additive EuroSCORE).

Table 1. Preoperative clinical characteristics and their impact on 30-day mortality according to univariate analysis and logistic regression

Clinical variables	No. (%)	Univariate analysis p-value	Logistic regression O.R. 95%C.I.
Age (years)	67.4±10.4	<0.0001	<0.0001, 1.076, 1.037–1.116
Females	944 (28.8)	0.001	
Pulmonary disease	352 (10.7)	<0.0001	0.001, 2.711, 1.485–4.948
Diabetes	618 (18.8)	0.001	
Cerebrovascular disease	348 (10.6)	0.001	
Neurological dysfunction	41 (1.3)	0.08	0.021, 4.631, 1.266–16.938
Extracardiac arteriopathy	251 (7.7)	0.005	
Serum creatinine (mmol/L)	94.0±49.4	<0.0001	
Renal failure	35 (1.1)	0.002	
Estimated glomerular filtration rate ml/min/1.73 m^2	74.5±19.5	<0.0001	0.003, 1.798, 1.044–3.096
Chronic kidney disease classification		<0.0001	
Classes 1–2	2573 (78.4)		
Class 3	668 (20.4)		
Classes 4–5	39 (1.2)		
Active endocarditis	19 (0.6)	0.001	
Myocardial infarction <3 months	626 (19.1)	<0.0001	
Previous cardiac surgery	120 (3.7)	<0.0001	
LVEF >50%	2180 (66.5)	<0.0001	
30–50%	967 (29.5)		0.34, 1.798, 1.044–3.096
<30%	133 (4.1)		0.071, 2.437, 0.927–6.407
Nitrates infusion at OR arrival	359 (10.9)	<0.0001	
Critical preoperative status	62 (1.9)	<0.0001	<0.0001, 8.274, 3.971–17.240
Systolic pulmonary a. pressure>60 mmHg	82 (2.5)	<0.0001	
Emergency operation	171 (5.2)	<0.0001	
Postinfarct ventricular septal rupture	9 (0.3)	<0.0001	
Additive EuroSCORE	4.8±3.1	<0.0001	
Logistic EuroSCORE (%)	5.9±8.7	<0.0001	

Continuous variables are reported as the mean±standard deviation; LVEF: left ventricular ejection fraction; OR: operating room O.R.: odds ratio.

Outcome prediction after isolated procedures

According to logistic regression CPBT, but not XCT, was associated with 30-day mortality among patients who underwent isolated procedures. However, the area under the ROC curve of CPBT was rather small (p=0.001, AUC: 0.64, 95%C.I. 0.58-0.71) compared to that of the overall series and of patients undergoing complex procedures.

Outcome prediction after complex procedures

Four hundred and twenty patients underwent two or more procedures on coronary arteries, heart valves, ascending aorta/aortic arch, and atrial or ventricular septum. ROC curve analysis showed that XCT (p<0.0001, AUC: 0.681, 95%C.I. 0.57-0.80), CPBT duration (p<0.0001, AUC: 0.74, 95%C.I. 0.64-0.85), and CPBT duration with unclamped aorta (p<0.0001, AUC: 0.79, 95%C.I. 0.70-0.88) were associated with 30-day postoperative mortality.

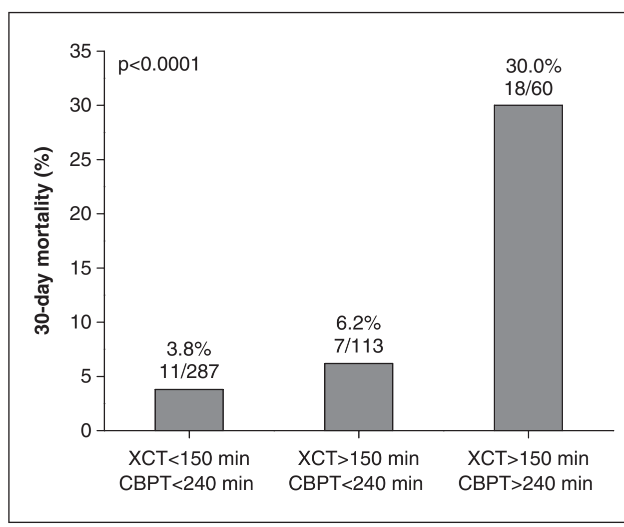

Figure 3. 30-day mortality rates after complex cardiac surgery according to different combination of cutoff values of aortic cross-clamping and cardiopulmonary bypass duration. P-value adjusted for additive EuroSCORE. XCT: aortic cross-clamping time. CPBT: cardiopulmonary bypass time.

Table 2. Operative and perfusion data and their impact on 30-day mortality according to univariate and multivariate analysis

Operative/perfusion variables	No. (%)	Univariate analysis p-value	Logistic regression p-value, O.R. 95%C.I.
Type of operation			
Isolated CABG	2422 (73.8)		
CABG + ventriculoplasty	15 (0.5)		
CABG + AVR	245 (7.5)		
CABG + MV surgery	72 (2.2)		
CABG + double valve surgery	20 (0.6)		
CABG + triple valve surgery	3 (0.1)		
CABG + other major cardiac procedures	9 (0.3)		
CABG + other non cardiac procedures	11 (0.3)		
Isolated AVR	236 (7.2)		
Isolated MV surgery ± ASD closure	124 (3.8)		
Double valve surgery	24 (0.7)		
Triple valve surgery	7 (0.2)		
Bentall-DeBono procedure ± CABG	50 (1.5)		
Other aortic procedures	2 (0.1)		
Tricuspid valve surgery + other procedures	3 (0.1)		
Isolated ASD closure	20 (0.6)		
Isolated VSD closure	4 (0.1)		
Other major cardiac procedures	13 (0.4)		
No. major cardiac procedures*		<0.0001	0.001, 2.43, 1.41–4.19
1	2820 (86.0)		
2	404 (12.3)		
3–4	56 (1.7)		
Surgery on the thoracic aorta	56 (1.7)	<0.0001	
Procedures other than isolated CABG	854 (26.0)	<0.0001	
Aortic cross-clamping time (min)	91±36	<0.0001	<0.0001, 0.97, 0.96–0.99**
Cardiopulmonary bypass duration (min)	117±48	<0.0001	<0.0001, 1.03, 1.02–1.04
Total potassium/magnesium administered through cardioplegia (ml); K^+ 1mmol/ml, Mg^{2+} 0.25mmol/ml	40.2±21.2	0.067	
Lowest cardioplegia temperature (°C)	28.3±2.1	0.18	
Maintenance cardioplegia temperature (°C)	28.9±1.9	0.19	
Crystalloid component of cardioplegia (ml)	493±253	0.006	
Lowest systemic temperature during CPB (°C)	32.9±1.5	<0.0001	
Highest plasma level of K^+ during CPB (mmol/l)	5.7±0.8	0.31	
Lowest hematocrit during CPB (%)	22±0.0	<0.0001	0.03, 0.92, 0.85–0.99

Continuous variables are reported as the mean±standard deviation; CPB: cardiopulmonary bypass; CABG: coronary artery bypass grafting; AVR: aortic valve replacement; MV: mitral valve; ASD: atrial septal defect; VSD: ventricular septal defect: *: We refer to isolated or multiple procedure according to the number of procedures on each major anatomical structure (coronary arteries, heart valves, ascending aorta/aortic arch, atrial or ventricular septum); **: Both cardiopulmonary bypass time and aortic cross-clamping time entered the regression model and correlation matrix showed their strong and negative correlation. For separate analysis refer to the results section.

When adjusted for additive EuroSCORE, XCT (p<0.0001, O.R. 1.01, 95%C.I. 1.01-1.02) and CPBT (p<0.0001, OR 1.01, 95%C.I. 1.01-1.02) were independent predictors of 30-day mortality among patients who underwent complex procedures. XCT>150 min (p<0.0001, OR 4.24, 95%C.I. 2.03-8.85) and CPBT>240 min (p<0.0001, OR 9.10, 95%C.I. 4.40-18.81) were associated with a highly increased risk of 30-day mortality. When their best cutoff values were adjusted for additive EuroSCORE, XCT>150 min (p=0.001, OR 4.13, 95%C.I. 1.82-9.37) and CPBT>240 min (p<0.0001, OR 4.81, 95%C.I. 2.13-10.86) were also associated with 30-day mortality in this high risk group. The effect of combining the cutoff values of these two risk factors is depicted in Figure 3 (p<0.0001 adjusted for additive EuroSCORE).

Severe postoperative complications

The rate of combined severe complications end-point (30-mortality, intensive care unit stay ≥ 5 days, stroke, postoperative use of IABP, and need of postoperative dialysis) was 10.9% (357/3280 patients). ROC curve analysis showed that XCT (p<0.0001, AUC: 0.644, 95%C.I. 0.61-0.68), CPBT duration (p<0.0001, AUC: 0.70, 95%C.I. 0.67-0.73), and CPBT duration with unclamped aorta (p<0.0001, AUC: 0.74, 95%C.I. 0.71-0.77) were associated with combined severe complications end-point. Figure 4 shows the

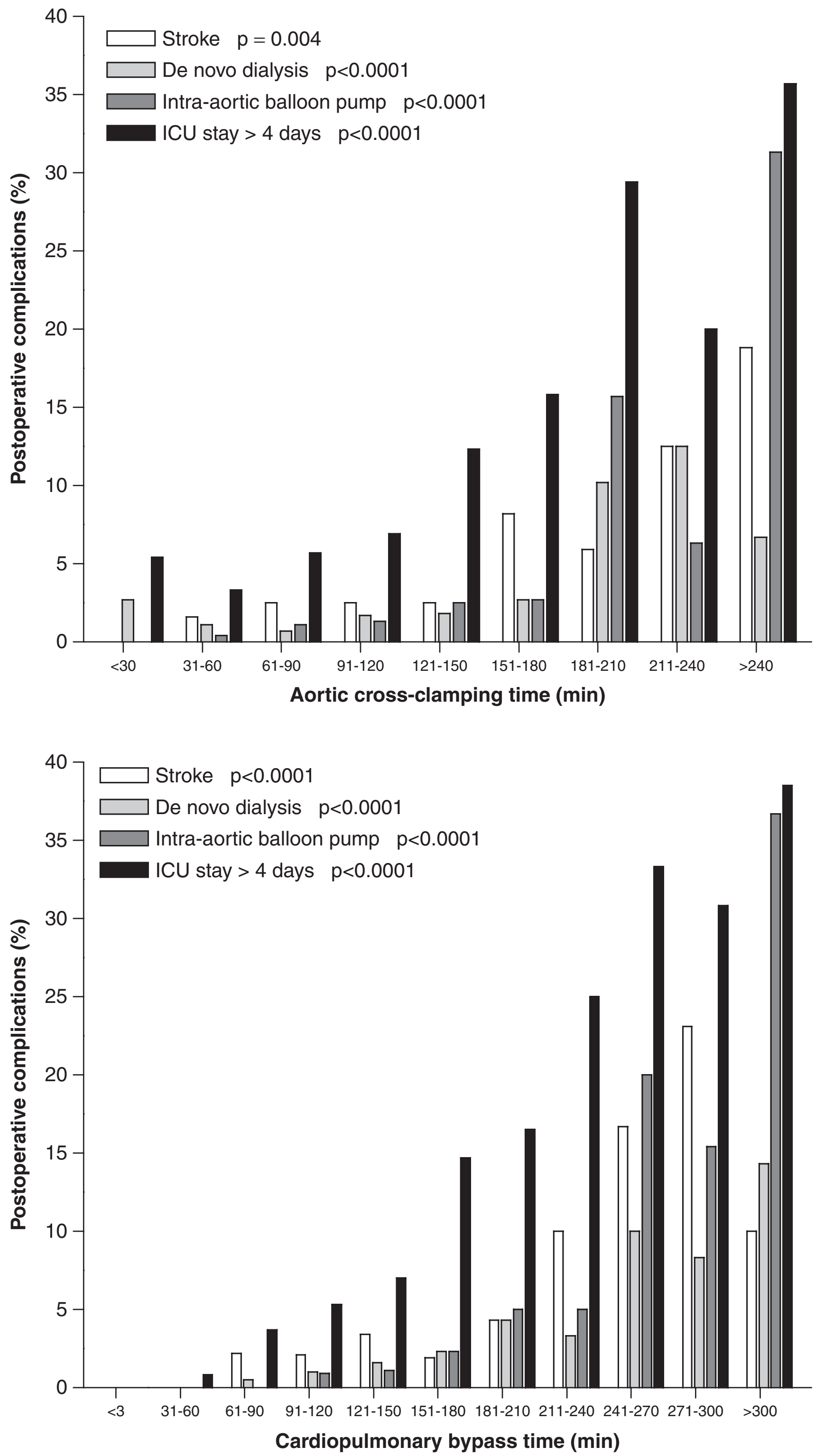

Figure 4. Rates of postoperative complications for increasing duration of aortic cross-clamping and cardiopulmonary bypass. P-values are adjusted for additive EuroSCORE.

rates of severe complications according to different XCTs and CPBTs as adjusted for additive EuroSCORE.

XCT correlated significantly with the amount of transfused red blood cell units (rho: 0.26, p<0.0001), the number of transfused homologous blood products (rho: 0.27, p<0.0001), time to extubation (rho: 0.136, p<0.0001) and length of stay in intensive care unit (rho: 0.19, p<0.0001). Likewise, CPBT correlated significantly with amount of transfused red blood cell units (rho: 0.31, p<0.0001), the number of transfused homologous blood products (rho: 0.32, p<0.0001), time to extubation (rho: 0.16, p<0.0001) and length of stay in intensive care unit (rho: 0.25, p<0.0001).

Discussion

The present findings confirm that the longer the XCT and CPBT the worse their detrimental effects will be.[7] This is mostly related to the well established systemic inflammatory response syndrome occurring after CPB[11] and myocardial ischemia occurring during cross-clamp.[12] However, the correlation between these parameters and adverse outcome is not straightforward. Indeed, it is rather difficult to discern the isolated, negative impact of myocardial ischemia and use of cardiopulmonary bypass from the patient's individual operative risk, intraoperative technical difficulties, as well as the surgeon's and anesthesist's skills and experience, and, last but not the least, the quality of postoperative care. Herein, we attempted to estimate the adverse effect of prolonged XCT and CPBT by multivariate analysis and by performing subanalyses in a series of patients who underwent cardiac surgery employing, contrary to other reports,[7] rather similar myocardial and non-cardiac organ protection strategies. We have observed that, with these methods and within safe CPBT and XCT intervals, i.e. CPBT<240 minutes and XCT<150 minutes, cardiac surgery can be performed with a rather low risk of postoperative mortality and morbidity independently of the patient's operative risk and the complexity of the procedure. It is worth noting that these time cutoff values, despite having a high accuracy (over 90%), have a rather low sensitivity. In such a large, complex and heterogenous patient population, we could not expect to have a sensitivity of 100% and a specificity of 100%. Since a significant number of patients having prolonged perfusion times will survive the operation, we could expect to have a large number of "true negatives", patients who do not experience such adverse end-points. In this sense, the herein reported cut-off values are predictive of true negatives under those threshold time limits, namely, prolonged CPBT and XCT do not automatically indicate a poor prognosis after the operation, rather that short CPBT and XCT are associated with very low risk of postoperative adverse events. Indeed, markedly long XCT and CPBT not univocally resulted in postoperative mortality.

This study also confirmed the marked impact of XCT and CPBT on postoperative morbidity, as is clearly shown in Figure 4. The strong association between postoperative stroke and XCT as well as CPBT is of particular interest. This is not a new finding as other authors[13,14] have shown that CPBT is an independent predictor of stroke, a severe complication which, by itself, has a significant impact on immediate and late mortality.[14] Brucerius and colleagues[13] have identified CPBT>2 hours as an independent predictor of postoperative stroke. This finding is rather similar to ours (Fig. 3). It seems that the safe CPBT for preventing postoperative stroke is much shorter than to prevent 30-day death. Not surprisingly, prolonged XCT also was significantly associated with an increased risk of postoperative stroke as it indicates more complex procedures, resulting in a prolonged CPBT.

Does CPBT have a more significant impact on the immediate outcome than XCT? There is a very strong correlation between these two parameters as shown by the correlation matrix of logistic regression. Because of this, we included these two variables separately into the final regression models. However, likelihood ratios showed that, in this series, CPBT was a much stronger predictor of 30-day mortality. Figure 1 shows that the correlation between XCT and CBPT with unclamped aorta was weaker than XCT and CPBT. ROC curve analysis confirmed these findings as CBPT with unclamped aorta had a larger area under the curve than XCT and CPBT in predicting 30-day postoperative death. Prolonged CPBT with unclamped aorta is a combination of perfusion time before cross-clamp and the reperfusion time after releasing the cross-clamp. A number of patients had prolonged CPBTs with unclamped aorta despite rather short XCTs. This may rather be related to critical preoperative condition of the patient or to technical difficulties than to ischemia and poor myocardial protection resulting in prolonged weaning from the CPB, particularly as there were many patients with long XCTs and relatively short CPBTs with unclamped aorta.

In conclusion, this study has shown that, in a series of patients who underwent adult cardiac surgery employing similar myocardial and non-cardiac organ protection techniques, XCT and CPBT were independent predictors of immediate postoperative morbidity and mortality. Based on our experience, cardiac procedures with CPBT<240 min and XCT<150 min were associated with a rather low risk of immediate postoperative adverse events.

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Is it possible to improve the accuracy of EuroSCORE?

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Abstract

Objective: We derived a new risk-scoring method by modifying some of the risk factors included in the EuroSCORE algorithm. **Methods:** This study includes 3613 patients who underwent cardiac surgery at the Vaasa Central Hospital, Finland. The EuroSCORE variables, along with modified age classes (<60 years, 60–69.9 years, 70–79.9 years and ≥80 years), eGFR-based chronic kidney disease classes (classes 1–2, class 3 and classes 4–5) and the number of cardiac procedures, were entered into the regression analysis. **Results:** An additive risk score was calculated according to the results of logistic regression by adding the risk of the following variables: patients' age classes (0, 2, 4 and 6 points), female (2 points), pulmonary disease (3 points), extracardiac arteriopathy (2 points), neurological dysfunction (4 points), redo surgery (3 points), critical preoperative status (8 points), left ventricular ejection fraction (>50%: 0; 30–50%: 2 and <30%: 3 points), thoracic aortic surgery (8 points), postinfarct septal rupture (9 points), chronic kidney disease classes (0, 3 and 6 points), number of procedures (1: 0; 2: 2 and 3 or more: 7 points). The modified score had a better area under the receiver operating characteristic curve (additive: 0.867; logistic: 0.873) than the EuroSCORE (additive: 0.835; logistic: 0.840) in predicting 30-day postoperative mortality. The modified score, but not EuroSCORE, correctly estimated the 30-day postoperative mortality. **Conclusion:** EuroSCORE still performs well in identifying high-risk patients, but significantly overestimates the immediate postoperative mortality. This study shows that the score's accuracy and clinical relevance can be significantly improved by modifying a few of its variables. This institutionally derived risk-scoring method represents a modification and simplification of the EuroSCORE and, likely, it would provide a more realistic estimation of the mortality risk after adult cardiac surgery.

Keywords: Aorta; Aortic valve; Coronary artery bypass surgery; Mitral valve; Risk; Surgery

1. Introduction

The prediction of the risk of adverse postoperative outcome is of paramount importance in cardiac surgery as it may guide the decision-making process whether to opt for cardiac surgery or for other currently available treatments. Furthermore, risk prediction allows for planning of resource utilisation, comparison between different institutions or surgeons and, least but not last, an estimate of the patient's individual risk.

During the last decades, several risk-scoring methods have been derived and validated with variable success [1]. Among these, the European system for cardiac operative risk evaluation (EuroSCORE) [2,3] is recognised as one of the most reliable risk-scoring method for prediction of immediate postoperative mortality [1]. It also seems to perform rather well in predicting late mortality [1,4,5]. Importantly, EuroSCORE is a simple, easy-to-use tool in the clinical field. Because of this, during the last few years, EuroSCORE has been extensively used for scientific and clinical purposes. However, the use of EuroSCORE as well as that of other risk-scoring methods is flawed by a significant overprediction of the mortality risk [1,6,7]. This may lead to a false sense of reassurance, underperformance may go undetected and patient welfare may be compromised [8]. Thus, any risk-scoring method in cardiac surgery should be both accurate and have a good predictive power.

In the present study, we evaluated the performance of EuroSCORE at our institution and derived a new risk-scoring method by modifying some of the risk factors originally included in the EuroSCORE algorithm.

2. Material and methods

This study includes a series of 3613 patients who underwent adult cardiac surgery at the Vaasa Central

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Hospital, Vaasa, Finland, from January 1994 to June 2008. The data on these patients were collected prospectively into an institutional cardiac surgery database. Only the first procedure for each patient was entered into the registry. Any other operation performed during the same in-hospital stay was not coded as a further procedure, but rather as a complication.

These patients belong to a series of 4563 patients who underwent cardiac surgery during the study period. The only exclusion criterion was the lack of preoperative data on creatinine and left ventricular ejection fraction. Patients who underwent isolated minor procedures such as pericardiectomy or for arrhythmias have been excluded as well. No attempt to replace missing values has been done.

The data on late death were retrieved from the National Registry of Statistics, Finland (Tilastokeskus).

2.1. Risk factor and definition criteria

Variables have been classified according to the EuroSCORE criteria [2].

The preoperative glomerular filtration rate was estimated according to the modified Modification of Diet in Renal Disease study equation [9,10]: eGFR (ml/min/1.73 m^2) = 186 $\times$ (serum creatinine (mg/dl))$^{-1.154}$ $\times$ (age)$^{-0.203}$ $\times$ 0.742 (if the subject is female) or $\times$1.212 (if the subject is black). The severity of renal failure was classified according to the chronic kidney disease (CKD) classification [9]: Class 1 (normal): eGFR $>$ 90 ml/min/1.73 m^2; Class 2 (mild): eGFR – 60–89 ml/min/1.73 m^2; Class 3 (moderate): eGFR – 30–59 ml/min/1.73 m^2; Class 4 (severe): eGFR – 15–29 ml/min/1.73 m^2 and Class 5 (kidney failure): eGFR $<$ 15 ml/min/1.73 m^2. We have entered three groups of patients into the regression analysis: Classes 1–2, Class 3 and Classes 4–5.

We have classified patients' age in four classes ($<$60 years, 60–69.9 years, 70–79.9 years and $\geq$80 years), as this classification was associated with a more evident increase in operative risk than the additive EuroSCORE age classes. Indeed, octogenarians and nonagenarians represent a relatively small number of high-risk patients whose age-related risk can be represented in only one class.

In the original EuroSCORE, non-coronary surgery was considered as a predictor of adverse outcome, despite the fact that patients with few or no co-morbidities may undergo any other isolated, major cardiac procedure without significantly higher mortality risk. In order to better estimate the impact of complex surgery on the immediate outcome, we have categorised major cardiac procedure as isolated, double or a combination of three or more procedures. This may reflect a longer cardiopulmonary bypass (CPB) duration and, not infrequently, more technically demanding procedures. Herein, we refer to isolated or multiple procedure according to the number of procedures for each major area (coronary arteries, heart valves, ascending aorta/aortic arch and atrial and ventricular septal defect). Surgery for cardiac tumours was considered as a type of major cardiac procedure. On the contrary, operations for arrhythmias or pericardial diseases were not classified as major cardiac procedures.

The method adopted for anaesthesia was combined general anaesthesia. Thoracic epidural anaesthesia (TEA) was used at the discretion of the anaesthesiologist for patients with anticipated pulmonary or other significant risks. Fentanyl 3–3.5 μg/kg, and propofol 0.8–2 mg/kg, were given intravenously for anaesthesia induction, followed by continuous infusion of propofol 1–2 mg/kg/h. Pancuronium 0.10 mg/kg was given for muscle relaxation. Clonidine 1.5–2 μg/kg was given as a slow intravenous bolus dose at the induction of anaesthesia to patients without TEA. The patients were ventilated with oxygen in air, fractional inspired oxygen (FiO_2) 0.4–0.5, supplemented with isoflurane or sevoflurane.

For CPB, we used a membrane oxygenator (Dideco Compactflo; Dideco S.p.A., Mirandola, Italy) with a non-pulsatile pump flow by means of a Stöckert roller pump (CAPS or SIII, Stöckert GMBH, Munich, Germany) or, from 2005, on a centrifugal pump (Stöckert SCP, Sorin Group Deutschland GMBH, München, Germany). Generally we have used a systemic temperature drift down to 32–34 °C. A 40-μm arterial line filter (D734, Dideco S.p.A.) was included in the CPB circuit. From 1994 to 2002, we used conventional non-coated PVC-tubings, but from 2002 we have routinely used a phosphorylcholine-coated bypass circuit (Ph.I.S.I.O., Dideco S.p.A.), and from 2005 on we have used a modified ECC.O mini-bypass circuit (Dideco S.p.A., Mirandola, Italy) in some of the cases. A blood cardioplegia technique was employed for cardiac protection in all cases. Cardiac arrest was initiated with a bolus dose of K/mg-cardioplegia concentrate solution given into a 35–37 °C warm mixture of a moderately hyperkalaemic 5% glucose solution and oxygenated blood was infused into the aortic root in a ratio of 1:8. The mixture was cooled to about 30 °C after cardiac arrest, and thereafter given as a continuous ante/retrograde infusion directly into the coronary ostia and/or through the coronary sinus and into the venous grafts. Before declamping of the aorta, the blood cardioplegia was warmed to 35–37 °C and infused for 4–5 min. The target activated clotting time was $\geq$600 s due to the use of a moderate dose of aprotinin (2.5–4 million units per patient).

2.2. Statistical analysis

Statistical analysis was performed using a SPSS statistical software (SPSS, version 14.0.1, SPSS Inc., Chicago, IL, USA). Continuous variables are reported as the mean $\pm$ standard deviation. The Pearson's chi-square, Fisher's exact, Kruskal–Wallis' and the Mann–Whitney's tests were used for univariate analysis. The receiver operating characteristics (ROC) curve was used to estimate the predictive value of continuous variables. The best cut-off values have been chosen according to the best sensitivity, specificity, accuracy and odds ratio. The Spearman's test was used to estimate the correlation of continuous variables. Logistic regression with the help of backward selection was used for multivariate analysis. The variables listed in Table 1 with a $p < 0.2$ at univariate analysis were included into the logistic regression model along with the year of operation. Additive and logistic scoring systems were then developed, the former having been calculated by adding rounded odds ratios. Additive and logistic EuroSCOREs were calculated according to the proposed formulas [2,3]. The Kaplan–Meier test and Cox's regression analysis were used to evaluate late survival. A $p < 0.05$ was considered statistically significant.

Table 1
Clinical characteristics and operative data.

	No. (%)	Univariate analysis *p*-value
Age (years)	67.7 ± 10.3	<0.0001
Age ≥70 years	1705 (47.2)	<0.0001
Females	1028 (28.5)	<0.0001
Pulmonary disease	404 (11.2)	<0.0001
Diabetes	695 (19.2)	0.004
Cerebrovascular disease	396 (11.0)	<0.0001
Extracardiac arteriopathy	304 (8.4)	<0.0001
Serum creatinine (mmol/l)	94.8 ± 49.4	<0.0001
Renal failure	41 (4.4)	0.003
Estimated glomerular filtration rate (ml/min/1.73 m^2)	74.3 ± 19.7	<0.0001
Chronic kidney disease classification		<0.0001
Classes 1—2	2815 (77.9)	
Class 3	753 (20.8)	
Classes 4—5	45 (1.2)	
Active endocarditis	19 (0.5)	0.001
Neurological dysfunction	47 (1.3)	0.028
Myocardial infarction <3 months	698 (19.3)	<0.0001
Previous cardiac surgery	158 (4.4)	<0.0001
LVEF >50%	2430 (67.3)	<0.0001
30—50%	1043 (28.9)	
<30%	140 (3.9)	
Nitrates infusion at OR arrival	397 (11.0)	<0.0001
Critical preoperative status	65 (1.8)	<0.0001
Systolic pulmonary a. pressure >60 mmHg	83 (2.3)	<0.0001
Emergency operation	186 (5.1)	<0.0001
Postinfarct ventricular septal rupture	9 (0.2)	<0.0001
Surgery on the thoracic aorta	56 (1.5)	<0.0001
Additive EuroSCORE	4.8 ± 3.1	<0.0001
Logistic EuroSCORE (%)	5.9 ± 8.4	<0.0001
Type of operation		
Isolated CABG	2750 (76.1)	
CABG + ventriculoplasty	15 (0.4)	
CABG + AVR	245 (6.8)	
CABG + MV surgery	72 (2.0)	
CABG + double valve surgery	20 (0.6)	
CABG + triple valve surgery	3 (0.1)	
CABG + other major cardiac procedures	9 (0.2)	
CABG + other non-cardiac procedures	13 (0.4)	
Isolated AVR	235 (6.5)	
Isolated MV surgery ± ASD closure	127 (3.5)	
Double valve surgery	24 (0.7)	
Triple valve surgery	7 (0.2)	
Bentall—DeBono procedure ± CABG	50 (1.4)	
Other aortic procedures	2 (0.1)	
Tricuspid valve surgery + other procedures	3 (0.1)	
Isolated ASD closure	20 (0.6)	
Isolated VSD closure	4 (0.2)	
Other major cardiac procedures	8 (0.2)	
Isolated major cardiac procedures	3152 (87.2)	<0.0001
Procedures other than isolated CABG	850 (23.5)	<0.0001

Continuous variables are reported as the mean ± standard deviation; CABG: coronary artery bypass grafting; AVR: aortic valve replacement; MV: mitral valve; ASD: atrial septal defect; and VSD: ventricular septal defect.

3. Results

3.1. 30-day postoperative mortality

The overall 30-day postoperative mortality rate was 2.5% (90 of the 3613). The 30-day postoperative mortality was not significantly different after isolated coronary artery bypass surgery (1.6%), isolated aortic valve surgery (1.7%) and isolated mitral valve surgery (2.5%) ($p = 0.75$). On the other hand, 30-day mortality rates after isolated procedure, double procedure and three to four procedures were 1.7% (54 of the 3152), 5.4% (22 of the 405) and 25% (14 of the 56), respectively ($p < 0.0001$). Accordingly, the CPB duration also correlated with the amount of procedures (106 ± 34 min, 172 ± 52 min and 262 ± 98 min, respectively, $p < 0.0001$).

The area under the ROC curve for predicting the 30-day mortality was much larger for the estimated preoperative glomerular filtration rate (0.716; 95% confidence interval (CI): 0.656—0.776; $p < 0.0001$) than for preoperative serum creatinine (0.660; 95%CI: 0.594—0.727; $p < 0.0001$). The 30-day mortality rate for CKD Classes 1—2 was 1.3%, for Class 3 it was 6.1% and for Classes 4—5 it was 13.3%, respectively ($p < 0.0001$), whereas it was 12.2% and 2.4% for patients with and without renal failure according to EuroSCORE criteria ($p = 0.003$). The estimated glomerular filtration rate, but not the preoperative serum creatinine, was an independent predictor of the 30-day mortality.

The patients' age, in all regression models, was an independent predictor of the 30-day mortality. When we evaluate age according to additive EuroSCORE criteria, marked difference in mortality was detected for patients aged 70 or older. However, a further increase was observed among octogenarians. Because of this factor, we have divided patient's age into four classes (30-day mortality rates: <60 years, 0.6%; 60—69.9 years, 1.8%; 70—79.9 years, 3.6%; ≥80 years, 4.6%, $p < 0.0001$).

Risk factors associated with the 30-day postoperative mortality at univariate, and at the final, regression analysis are listed in Tables 1 and 2. The Hosmer—Lemeshow chi-square of the final regression model was 4.952, $p = 0.763$.

The ROC analysis showed that the modified score had a slightly better area under the curve (additive: 0.867, 95%CI: 0.830—0.904; logistic: 0.873, 95%CI: 0.837—0.909) than the EuroSCORE (additive: 0.835, 95%CI: 0.790—0.879; logistic: 0.840, 95%CI: 0.796—0.883) (Fig. 1) for prediction of the 30-day postoperative mortality. Similar areas under the ROC curve were observed in predicting in-hospital mortality (area under the ROC curve: additive modified score 0.867, 95%CI: 0.832—0.902; logistic modified score 0.872, 95%CI: 0.838—0.907; additive EuroSCORE 0.831, 95%CI: 0.788—0.873; logistic EuroSCORE 0.836, 95%CI: 0.794—0.878).

Such marginal superiority of the modified score shown by ROC analysis became much more significant when we compared the observed and predicted 30-day mortality along different additive scores. In fact, EuroSCORE was associated with a large difference between the predicted and observed mortality, whereas the modified score provided predicted mortality rates much closer to the observed ones (Fig. 2).

3.2. Outcome prediction after isolated major procedures

The modified risk score performed somewhat better than EuroSCORE in predicting the 30-day mortality after isolated coronary artery bypass surgery (area under the ROC curve: additive modified score — 0.818, 95%CI: 0.759—0.876; logistic modified score — 0.819, 95%CI: 0.761—0.877; additive

Table 2
Results of logistic regression in predicting 30-day postoperative mortality.

	Beta-coefficient	Standard error	*p*-value	Odds ratio	95% confidence interval	Additive score points
Patients' age						
<60 years			0.005			
60–69 years	0.779	0.571	0.173	2.178	0.711–6.674	2
70–79 years	1.371	0.550	0.013	3.940	1.340–11.588	4
≥80 years	1.853	0.606	0.002	6.377	1.944–20.923	6
Female	0.536	0.263	0.042	1.709	1.020–2.863	2
Pulmonary disease	1.080	0.280	0.000	2.945	1.700–5.101	3
Extracardiac arteriopathy	0.778	0.320	0.015	2.178	1.164–4.075	2
Neurological dysfunction	1.461	0.615	0.018	4.309	1.290–14.398	4
Redo surgery	1.049	0.385	0.006	2.855	1.343–6.070	3
Critical preoperative status	2.079	0.371	0.000	7.993	3.860–16.552	8
Left ventricular ejection fraction						
>50%			0.001			
30–50%	0.870	0.262	0.001	2.387	1.429–3.986	2
<30%	1.102	0.461	0.017	3.010	1.218–7.436	3
Surgery of the thoracic aorta	2.115	0.549	0.000	8.287	2.825–24.305	8
Ventricular septal defect secondary to myocardial infarction	2.219	0.777	0.004	9.197	2.005–42.192	9
Chronic kidney disease classification						
Classes 1–2			0.000			
Class 3	0.995	0.263	0.000	2.704	1.615–4.527	3
Classes 4–5	1.858	0.586	0.002	6.413	2.035–20.211	6
Number of procedures						
1			0.000			
2	0.736	0.306	0.016	2.089	1.146–3.807	2
3–4	1.882	0.489	0.000	6.567	2.516–17.139	7
Constant	−6.779	0.567	0.000	0.001		

EuroSCORE – 0.781, 95%CI: 0.710–0.853; logistic EuroSCORE – 0.785, 95%CI: 0.714–0.855).

The modified risk score as well as EuroSCORE performed extremely well in predicting the 30-day mortality after isolated aortic valve surgery (area under the ROC curve: additive modified score – 0.946, 95%CI: 0.898–0.993; logistic modified score – 0.964, 95%CI: 0.932–0.997; additive EuroSCORE – 0.908, 95%CI: 0.844–0.971; logistic EuroSCORE – 0.936, 95%CI: 0.893–0.980). When both additive scores were divided in quartiles, mortality occurred only in the last quartiles, that is, additive scores ≥8 (EuroSCORE: observed 30-day mortality 8.2%, mean expected mortality 15.9 ± 9.9%; modified score: observed 30-day mortality 6.6%, mean predicted mortality 5.3 ± 6.9%).

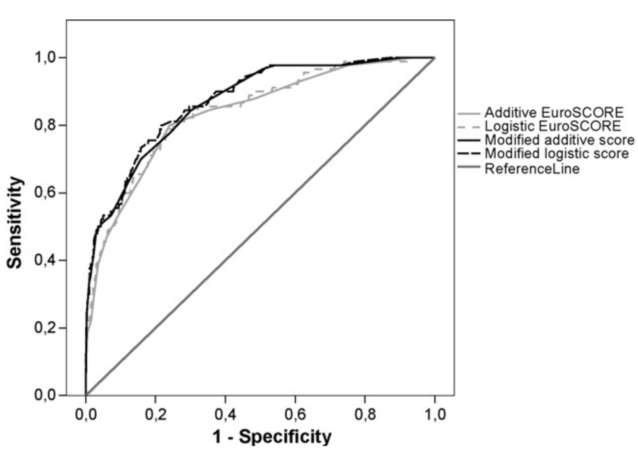

Fig. 1. Receiver operating characteristics curves of additive and logistic EuroSCORE and modified score in predicting 30-day postoperative mortality after adult cardiac surgery.

The modified risk score performed well also in predicting the 30-day mortality after mitral valve surgery (area under the ROC curve: additive modified score 0.877, 95%CI: 0.805–0.950; logistic modified score: 0.907, 95%CI: 0.850–0.964). The EuroSCORE tended, likewise, to be a valid predictor of postoperative mortality after isolated mitral valve surgery (area under the ROC curve: additive EuroSCORE 0.801, 95%CI: 0.505–1.096; logistic EuroSCORE: 0.832, 95%CI: 0.605–1.058).

3.3. Severe postoperative complications

The combined adverse end-point (30-day mortality, intensive care unit stay ≥5 days, stroke, postoperative use of intra-aortic balloon pump and the need of postoperative dialysis) was observed in 383 patients (10.6%). Both risk-scoring methods were good predictors of combined end-point (area under the ROC curve: additive modified score – 0.782, 95%CI: 0.760–0.807; logistic modified score – 0.786, 95%CI: 0.762–0.810; additive EuroSCORE – 0.748, 95%CI: 0.722–0.774; logistic EuroSCORE – 0.752, 95%CI: 0.726–0.778).

3.4. Long-term outcome

The modified score had a somewhat better area under the ROC curve (additive: 0.841, 95%CI: 0.810–0.872; logistic: 0.849, 95%CI: 0.818–0.879) compared to the EuroSCORE

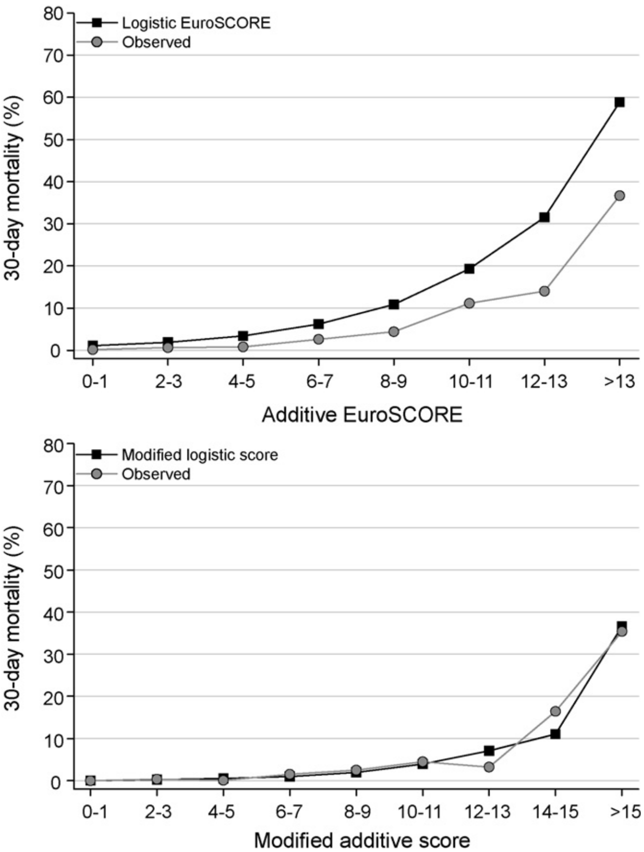

Fig. 2. Observed and predicted postoperative mortality according to the logistic EuroSCORE and the logistic modified score in different additive modified score classes and additive EuroSCORE classes.

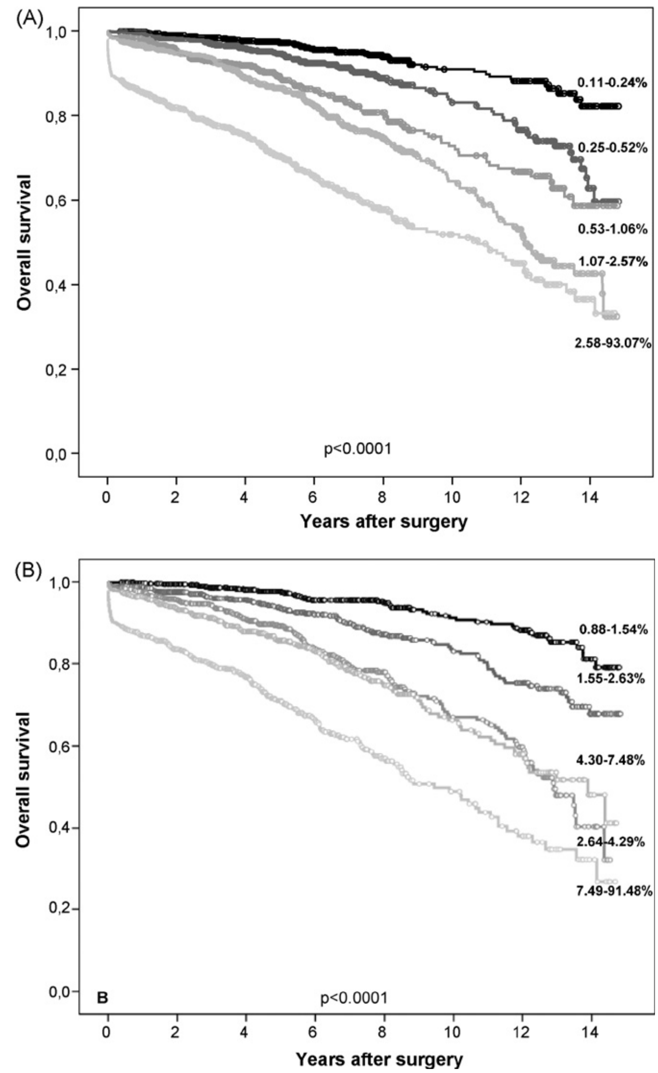

Fig. 3. Kaplan—Meier's estimates of overall survival after adult cardiac surgery according to quintiles of logistic modified score (A) and logistic EuroSCORE (B).

(additive: 0.807, 95%CI: 0.771—0.844; logistic: 0.815, 95%CI: 0.780—0.851) in predicting overall mortality at 1 year.

According to Cox's survival analysis, both scoring methods were good predictors of all-cause late mortality (when both scoring methods were included into the regression analysis: additive modified score — relative risk (RR): 1.132, 95%CI: 1.099—1.167; additive EuroSCORE — RR: 1.091, 95%CI: 1.055—1.129). Similar results were achieved when only operative survivors were included in the analysis. Fig. 3 shows the Kaplan—Meier's estimates of overall survival according to logistic modified score and the logistic EuroSCORE quintiles.

4. Discussion

The evaluation of EuroSCORE in our institutional database showed that it is a rather accurate tool for risk stratification of 30-day and long-term mortality after adult cardiac surgery. However, this study confirms its previously observed pitfalls in estimating immediate postoperative mortality rate of these patients [1]. This issue is of great clinical importance at present as new, less invasive surgical procedures as well as percutaneous and medical treatments can be offered as alternative therapies in high-risk patients. However, an overestimation of the operative risk would lead to an indication of less invasive treatment methods in patients who could have better immediate and/or late results with traditional surgical procedures. This applies particularly to treatment methods such as transcatheter aortic valve implantation [7] and percutaneous coronary interventions [11], whose durability, so far, is inferior to traditional surgical treatments.

The risk-scoring method developed for the present study demonstrates that the modification of a few risk factors included in the EuroSCORE may markedly improve its predictive power. In particular, the introduction of estimated glomerular filtration rate and a better classification of the complexity of surgery seem to provide a better estimation of the operative risk.

Renal failure is recognised as one of the most powerful predictors of outcome after cardiovascular surgery, and estimated glomerular filtration rate seems to be superior to serum creatinine for operative risk estimation [12,13]. Importantly, estimated glomerular filtration rate may be useful to identify those patients with subclinical renal failure who may benefit from early referral to a nephrologist [14]. Its use in cardiac surgery would lead to a better identification and prompt treatment of patients who are at risk of developing late renal failure.

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The complexity of cardiac surgery is *per se* a major determinant of adverse outcome. This is related not only to a longer operative time and CPB duration, but also to technical aspects and their related complications. However, it is difficult to quantify the complexity of the procedure as it can be multifactorial, with the results, possibly, being related to the surgeon's experience and skills. We believe that the variable 'other than isolated coronary artery bypass surgery' as defined by EuroSCORE is likely to consider several isolated procedures as complex cardiac surgery though not having a significantly higher mortality risk than isolated coronary surgery. We attempted to redefine this variable including three classes of procedures which should correlate better with the complexity of cardiac surgery. Indeed, when both variables were included into the regression analysis, only the amount of procedures/areas of intervention was an independent predictor of the 30-day mortality. It is worth noting that performing three or more interventions (e.g., double valve surgery plus coronary surgery, replacement of the ascending aorta and aortic valve plus coronary surgery) is associated with a rather high odds ratio. Interestingly, despite such findings, aortic surgery was still an important, independent predictor of postoperative mortality.

In our regression model, some EuroSCORE variables such as emergency surgery and nitrates infusion at operating-room arrival were not predictive of adverse outcome. This can be explained by the subjective nature and the influence of logistic factors in defining these two variables. Undoubtedly, most of patients requiring emergency surgery and/or nitrates infusion have an increased operative risk, but certainly not all of them. Similarly, recent myocardial infarction was also not an independent predictor of postoperative mortality. This could be due to the large heterogeneity of patients having a myocardial infarction within the 3 months prior to the surgery. The transmural and subclinical myocardial infarctions lie within this group. Furthermore, it is not unusual to detect a small increase of troponin levels just prior to elective surgery in asymptomatic patients without history of myocardial infarction. Other risk factors such as left ventricular ejection fraction and critical preoperative state are probably more representative for the most clinically relevant myocardial infarctions.

This study has several limitations. The first is that the study subjects have been operated across a long period of time, during which changes in treatment methods and in patients' operative risk have certainly occurred. We attempted to control for such a possible bias by including the year of operation into the logistic regression analysis. The second limitation is the small size of the study which, we believe, does not allow division into sufficiently large derivation and validation datasets. The third is the possibility of errors in defining clinical variables in the pre-EuroSCORE era. However, such a risk should be minimal as all variables were originally and prospectively classified according the Higgins' risk-scoring method [15].

In conclusion, EuroSCORE still performs very well in identifying high-risk patients. Its main pitfall is the overestimation of immediate postoperative mortality. This study shows that its accuracy and clinical relevance can be significantly improved by modifying a few of its variables in the light of current knowledge on predictors of poor outcome after cardiac surgery. The institutionally derived risk-scoring method presented in this article represents a modification and simplification of the EuroSCORE which could provide a more realistic estimation of the mortality risk after adult cardiac surgery during the immediate postoperative period.

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